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13. ABSTRACT (Maximum 200 Words)

We propose a training grant to recruit and train two postdoctoral students and three physicians, but have been able to extend that number to four postdoctoral students and four physician trainees. These trainees will acquire skills in the epidemiology and prevention of breast cancer. They will work closely with mentors who have a long track record of training epidemiologists. The funding will allow our research group to focus specific training opportunities on breast cancer. The ongoing epidemiologic studies and prevention trials offer a unique resource in which trainees can participate in cutting edge research and acquire skills that will establish them as future leaders. We have to date enrolled four doctoral students: Heather Baer, Heather Eliassen and Jeanne Marie Gaare-Eby, and Sonia Mathews; and four physicians: Ann Partridge, M.D. received her M.P.H. Larissa Nekhlyadov, M.D., M.P.H., this past year, has been pursuing several research projects in breast cancer prevention and early detection; Candice Aitken, M.D., received her M.P.H. and Erica Mayer, M.D. will pursue her M.P.H. with the support of this grant. As a result of this award, we have also established the Advanced Cancer Epidemiology Seminar each spring in which allows specialized topics to be explored in depth.

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INTRODUCTION

We have proposed a training grant to recruit and train two doctoral students and three physicians. In analyzing the budget going into the final year we requested an extension of one year to finish spending on the grant. Last year we anticipated carryover and so recruited an additional postdoctoral student and for this upcoming year extension we have another doctoral student and a physician MPH candidate. These trainees will acquire skills in the epidemiology and prevention of breast cancer. They will work closely with mentors who have a long track record of training epidemiologists. The funding will allow our research group to focus specific training opportunities on breast cancer. The ongoing epidemiologic studies and prevention trials offer a unique resource in which trainees can participate in cutting edge research and acquire skills that will establish them as future leaders.

BODY

(Approved Statement of Work is italicized)

*We will advertise and recruit **one pre-doctoral candidate** for the first year of this proposed training program.* We did not recruit in the first year (year one was expected to begin 7/1/00) due to funding not being received until September 2000 we were delayed in starting the recruitment process.

*We will advertise and recruit **one physician for a two-year training** opportunity that includes course work in the first year and research on one of the ongoing studies in the second year.* We recruited Dr. Ann Partridge, MD whose research focuses on the assessment, perception and communication of breast cancer risk as well as other aspects of provider-patient communication in oncology. She earned her M.P.H. while being supported by this fellowship.

*We will recruit **a second pre-doctoral candidate** to begin training in the second year.* We have recruited two pre-doctoral students, Heather Baer and Heather Eliassen, to make up for the first year. During the past year, Ms. Baer did publish her findings on adolescent diet and benign breast disease[4] and has made further progress on her research in the field of breast cancer etiology and prevention, and is nearing completion of her doctoral thesis. Her thesis research focuses on identifying factors in early life, childhood, and adolescence that influence subsequent risk of breast cancer and benign breast disease. She is using data from the Nurses' Health Study and the Nurses' Health Study II to conduct this research. She recently presented the findings from her first thesis project, "Body fatness at young ages and incidence of premenopausal breast cancer," at the Nurses' Health Study External Advisory Board Meeting and at the annual meeting of the Society for Epidemiologic Research. She recently completed this manuscript and will be submitting it to the Journal of the National Cancer Institute[5]. She is in the process of writing another manuscript, "Early life factors and incidence of benign breast disease," and will be submitting this for publication within the next few months. Finally, she has begun the analysis for a third manuscript, "Childhood socioeconomic status in relation to age at menarche and breast cancer risk," and will be writing the manuscript in the late summer and early fall. She is planning to defend her thesis in November of 2004. In addition to her thesis research, she has worked with Dr. Graham Colditz, on several other projects. In particular, she has assisted with the collection and analysis of data and preparation of manuscripts for a nested case-control study of benign breast lesions as markers of breast cancer risk[6], which involves collaboration with several breast pathologists at Beth Israel-Deaconess Medical Center. She has also worked on the preparation of a chapter about breast cancer for a cancer epidemiology textbook[7], the data analysis and preparation of a manuscript on the assessment of diet among low-income Native American and Caucasian pregnant women, the preparation of a renewal for a grant to examine predictors of benign breast disease and risk factors for breast cancer among women with benign breast disease, and the preparation of a short grant proposal to examine the relationship between childhood adiposity and concentrations of sex hormones in girls.

Ms. Eliassen's training this year focused on her dissertation. Her dissertation addresses potential lifestyle factors that may lower risk of breast cancer . The first paper addresses the association between use of the statin family of lipid-lowering drugs and breast cancer. I submitted an abstract and presented my work on this topic at a symposium titled Breast Cancer Research at Harvard[8]. I have completed the manuscript, and will soon submit it for publication. Her second paper addresses the relation of tubal sterilization with incidence of breast cancer[9]. I submitted an abstract on this topic to the annual Society for Epidemiologic Research meeting· I traveled to Salt Lake City for the annual meeting in June 2004 to present a poster on my analysis thus far. I have written a draft of the manuscript, and plan to submit it for publication this fall. . I have also My final topic addresses the association between weight gain and loss in adult life and incidence of breast cancer. I have begun analyses on this last topic, and plan to write up a manuscript this fall. I have also worked with my advisor, Dr. Susan Hankinson, on analyses on sex steroid hormones[10], prolactin[11], and breast cancer incidence. She will be second author on two papers from this work. I plan to defend my dissertation this fall, and graduate in November 2004.

We are now entering the last year of the grant and after a budget analysis resulting in an extension, we recruited a third (reported previously) Jeanne Marie Gaare-Eby and a fourth to take advantage of this fellowship, Sonia Mathews. Ms. Gaare-Eby has been taking courses for doctoral program in epidemiology at HSPH. She has also been involved in research on benign breast disease, specifically looking at the relationship between fibroadenomas and papillomas and the risk of benign breast disease in the Nurses' Health Study II cohort.
Sonia Mathews' major research interests involve studying the effects of diet, physical activity, and obesity – as they occur in adolescence and adulthood – and their subsequent impact on breast cancer. She is also interested in applying knowledge generated from research toward public health prevention strategies. To date, she has completed her second year as a doctoral student and has taken classes to fulfill her program course requirements. In addition to taking classes, she has been working on one of her thesis papers. This research work, which is still ongoing, involves testing the validity and reproducibility of a food frequency questionnaire (High School FFQ) in a subgroup of the Nurses' Health Study II (NHSII) cohort. Her responsibilities thus far for this research work have included overseeing all aspects of this 1473-subject study including obtaining IRB approval, coordinating survey and reminder mailings, and contacting subjects. The following is an update of activities related to this research that she has completed or that are still in progress for this academic year: She has completed data collection for three groups of participants: the members of NHSII, their mothers and their offspring; Completed the data analysis for one of two manuscripts related to this study; Presented results of analysis at the "Breast Cancer Research at Harvard Symposium"; Wrote abstract for the "Breast Cancer Research at Harvard Symposium"[12], which was accepted; Submitted manuscript to the American Journal of Epidemiology[13] (She is currently in the process of re-submitting a revised manuscript, responding to feedback from the editor); Presently, she is analyzing data for a second manuscript related to this study; she is also in the process of defining two other thesis paper topics for my doctoral program and determining their feasibility.

During the second year we will advertise for ***two physicians*** *to begin training in the third year.*
We successfully recruited Dr. Larissa Nekhlyudov and Dr. Candice Aitken (three so far) and additionally, a fourth one for a year of support towards her M.P.H., Erica Meyer, M.D. who's research interests involve working with the breast oncology center at Dana Farber Cancer Institute where she plans to focus on treatment of breast cancer in the elderly. She is considering projects working with the National Comprehensive Cancer Network (NCCN) database, clinical trials through the DFCI/Harvard Cancer Center and possibly translational work with a lab colleague.

Dr. Larissa Nekhlyudov, this year continued to work in the area of women's decision making in breast cancer prevention and early detection. The DOD fellowship specifically supported my work on studying the health related quality of life (HRQoL) among women with ductal carcinoma in situ (DCIS) of the breast. This study investigates prospectively using the Nurses' Health Study population, the HRQoL in women diagnosed with DCIS. Our early results suggest that the DCIS diagnosis does not have detrimental effects on women's overall HRQoL; however, there may be some short-term declines. She presented these results at the national meeting of the Society of General Internal Medicine held in Chicago in May 2004[1]. Her oral presentation was nominated for best presentation by junior faculty. Additional analyses are currently underway and a manuscript will be submitted by October 2004. The fellowship also helped support her effort in developing and submitting an R01-equivalent research proposal to the American Cancer Society in October 2003 (resubmitted in April 2004). The goal of the proposal is to develop an effective means of communicating information to women about breast cancer screening. In addition to the above projects, She is the lead investigator on two studies, one addressing screening mammography among women in their 40's, the other is aiming to improve the management of breast symptoms by primary care providers. She is also a co-investigator on two NCI-funded studies determining the predictors of DCIS recurrence and patient-oriented outcomes of prophylactic mastectomy.

The other physician recruited to begin last year is Dr. Candice Aitken, received her Masters in Public Health, Clinical Effectiveness Pathway. Working with Dr. Graham Colditz, she sought to use the Nurses Health Study database to discover possible risk factors for the development of estrogen receptor negative breast cancers. In collaboration with Marco Romani and Delin Shen, they ran exploratory analysis to search for a correlation between data collected in the NHS and the development of an ER negative breast cancer.

No conclusive risk factors were determined as of yet. This work is still ongoing. She also sought to develop an algorithm for use in the primary care setting to help a woman determine her particular risk of breast cancer using known personal parameters compared against the Colditz and Rosner cumulative risk of breast cancer to age 70 model. Again with Marco Romani and Delin Shen, they sought to use Bayesian analysis to predict the most important predictors of breast cancer risk. They identified the following four inputs: oral contraceptive use duration, family history, BMI slope and history of benign breast disease. They are in the process of refining the analysis and preparing an abstract for submission to ASCO (Dec 2004) and also a manuscript for publication. Working with Dr. Harvey Mamon, she designed and wrote a protocol that seeks to use stereotactic body radiotherapy in the treatment of liver metastases. She attended the 2nd and 3rd annual SBRT meetings to learn about the work being performed by other groups in this area of research. The protocol had been approved by the IRB at the Harvard Cancer Center and has been activated. She will be attending a training session in Wurzburg, Germany to use the stereotactic body frame and treat patients with this highly conformal technique. In addition, she is working on a new protocol to use this technology in the treatment of stage I medically inoperable lung cancer. Together with Dr. Harvey Mamon, they wrote a review article for publication in Hematology and Oncology summarizing the current literature on sphincter-sparing therapy for rectal cancer[2]. This was published in Dec 2003. Working with Dr. Anthony D'Amico, she evaluated endorectal MRI in a PSA-screened population. This work was submitted in abstract form to ASTRO and was accepted for a poster presentation[3]. This work was the focus of my resident seminar. The preparation of the manuscript is in progress and will be submitted for publication in the coming weeks

During the first year ***we will develop and implement an advanced seminar in breast cancer****. This will bring new depth to course work not previously available at the Harvard School of Public Health. This seminar will cover topics in detail and will span from basic biology of the breast, to early lesions, epidemiologic risk factors, statistical models of breast cancer incidence and issues in risk stratification and counseling for prevention.* Going into the second year of the grant, an eight-week seminar was developed and implemented specifically for breast cancer epidemiology, covering such topics as modeling breast cancer risk, postmenopausal hormones and breast cancer, gene environment interactions and benign breast disease. It was attended by Heather Baer, Heather Eliassen and Dr. Partridge and Dr. Nekhlyudov, along with other breast cancer researchers. This past spring Dr. Colditz again organized and led this course. Topics in the past covered mathematical models of breast carcinogenesis, associations between endogenous and exogenous hormones and breast cancer, histopathology of benign and malignant breast conditions, estrogen receptivity of tumors, breast morphology (mammographic density), mechanisms of chemoprevention and public health implications of such a strategy, lifestyle factors, (diet and physical activity) and breast cancer, mammographich screening and risk communication. This spring seminar has been established and will evolve into discussions on specific topics on regarding other cancers.

KEY RESEARCH ACCOMPLISHMENTS IN REFERENCE TO STATEMENT OF WORK

- We have successfully recruited and trained two doctoral fellows as is stated in the statement of work. Because of the projected carry-forth and extension granted on our period of performance we have successfully recruited another doctoral fellow, Sonia Mathews, making four supported by this grant. Ms. Mathews' major research interests involve studying the effects of diet, physical activity, and obesity – as they occur in adolescence and adulthood – and their subsequent impact on breast cancer. She is also interested in applying knowledge generated from research toward public health prevention strategies. To date, she has completed her second year as a doctoral student and has taken classes to fulfill her program course requirements.
- We have also successfully recruited four physician trainees all together. Three have completed their training and two were awarded their M.P.H. degrees while being supported by this fellowship, and now Erica Meyer, MD, with one year of support, is enrolled and is working towards her M.P.H. Dr. Meyer's research interests involve working with the breast oncology center at Dana Farber Cancer Institute where she plans to focus on treatment of breast cancer in the elderly. She is considering projects working with the National Comprehensive Cancer Network (NCCN) database, clinical trials through the DFCI/Harvard Cancer Center and possibly translational work with a lab colleague.
- The Advanced Cancer Epidemiology Seminar in Breast Cancer was established as a result of this award. Trainees and other students attend and it will remain as an advanced seminar in cancer.

REPORTABLE OUTCOMES

- Dr. Larissa Nekhlyudov, presented results to the Society of General Internal Medicine held in Chicago, May 2004. The presentation is entitled "Effects of Ductal Carcinoma in Situ on Quality of Life: Results from the Nurses' Health Study"[1].
- This was nominated best presentation for junior faculty.
- Dr. Nekhlyudov developed and submitted a research grant to the American Cancer Society in October 2003 (resubmitted April 2004). The goal of the proposal is to develop an effective means of communicating information to women about breast cancer screening.
- Dr. Nekhlyudov is the lead investigator on two studies, one is addresses screening mammography among women in their 40's, the other is aiming to improve the management of breast symptoms by primary care providers. She is also co-investigator on two NCI-funded studies determining the predictors of DCIS recurrence and patient-oriented outcomes of prophylactic mastectomy.
- Dr. Candice Aitken received her M.P.H. June. 2004.
- Dr. Aitken has written a protocol and has been IRB approved to do a study that seeks to use stereo static body radiotherapy in the treatment of liver metastases. She attended the 2nd and 3rd annual SBRT meetings to learn about the work being performed by other groups in this area of research. She will be attending a training session in Wurzburg, Germany to use the stereostatic body frame and treat patients with this highly conformal technique.
- Dr Aitken has co-written a review article summarizing the current literature on sphincter-sparing therapy for rectal cancer[2].
- Dr. Aitken presented a poster to American Society for Therapeutic Radiation Oncologists (ASTRO) evaluating endorectal MRI in a PSA-screened population[3].
- Ms. Heather Baer published a paper as first author on adolescent diet and benign breast disease[4].
- Ms. Heather Baer submitted an abstract regarding body fatness at young ages and incidence of premenopausal breast cancer[5].
- Ms. Heather Baer was a contributing author on a paper concerning diet and benign breast disease[6].
- Ms. Heather Baer also contributed to a book chapter [7].
- Ms. Heather Baer presented a poster at Harvard Breast Cancer Research Symposium, April 9, 2004: *Body fatness at young ages and incidence of premenopausal breast cancer*
- Ms.Heather Baer presented orally at Nurses' Health Study External Advisory Board Meeting, April 21, 2004: *Body fatness at young ages and incidence of premenopausal breast cancer*
- Ms. Heather Baer also presented orally at the Society for Epidemiologic Research (SER) annual meeting, June 18, 2004: *Body fatness at young ages and incidence of premenopausal breast cancer.*
- Ms. Eiassen submitted an abstract and submitted her work which addresses the association between use of the statin family of lipid-lowering drugs and breast cancer[8].
- Ms. Eliassen wrote a second paper which addresses the relation of tubal sterilization with incidence of breast cancer. She submitted an abstract on this topic to the annual Society for Epidemiologic Research meeting[9]. She travelled to Salt Lake City for the annual meeting in June 2004 to present a poster.
- Ms. Eliassen's final topic addresses the association between weight gain and loss in adult life and incidence of breast cancer. She has begun analyses on this last topic, and plan to write up a manuscript this fall.
- Ms. Eliassen has worked on analyses on sex steroid hormones[10], prolactin[11], and breast cancer incidence. She will be second author on two papers from this work.
- Ms. Sonia Mathews had an abstract accepted to "Breast Cancer Research at Harvard" Symposium[12].
- Ms. Sonia Mathews submitted a manuscript entitled "Adult Recall of Adolescent Diet: Reproducibility and Comparison with Maternal Reporting " to the American Journal of Epidemiology[13].
- She has completed data collection for three groups of participants: the members of NHSII, their mothers and their offspring; Completed the data analysis for one of two manuscripts related to this

study and presented results of the analysis at the "Breast Cancer Research at Harvard Symposium".

- Ms. Mathews is analyzing data for a second manuscript related to this study.
- Ms. Mathews is in the process of defining two other thesis paper topics for her doctoral program and determining their feasibility.

CONCLUSIONS

Our trainees in breast cancer epidemiology and prevention are proving to be exceptional researchers. As a result of this award, trainees graduate with advanced degrees in epidemiology from HSPH and the resources of the on-going epidemiologic research at the Brigham and Women's Hospital are providing excellent training opportunities for more in depth breast cancer epidemiology and prevention.
As a result of this training award, we have achieved our goal of training professionals in translational research.

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Background

The incidence of ductal carcinoma in situ (DCIS) of the breast has been rising, attributable mostly to screening mammography, and now accounts for about 20% of breast cancer diagnoses. Some have expressed concern with the possibility of overdiagnosis and the subsequent adverse effects on quality of life. However, the effect of DCIS on a woman's quality of life is not known. We therefore undertook a study to determine the quality of life in women before and after a diagnosis of DCIS.

Methods

The study included 149,398 women from the Nurses Health Study I (recruited in 1976) and Nurses Health Study II (recruited in 1989) who completed the Short Form 36 (SF-36), a health-related quality of life (HRQoL) assessment, in 1992-3 and 1996-7. All women were free of cancer at the time of entry; 433 cases of DCIS were diagnosed between 1992 and 1997. Analyses were conducted using PROC GLM linear regression, adjusting for age, treatment type and/or patient characteristics.

Results

HRQoL scores at baseline and 4-year follow-up were similar among women with and without DCIS. However, women who completed the SF-36 surveys within 6 months of diagnosis of DCIS experienced clinically (though not statistically) significant declines (~5 points) in four HRQoL domains including role limitations due to physical problems, bodily pain, vitality and social functioning but not in physical functioning or mental health. Declines in HRQoL disappeared within one year of diagnosis. There were no differences in HRQoL by type of treatment received.

Conclusion

Women diagnosed with DCIS may experience clinically significant declines in health-related quality of life shortly after diagnosis but rebound quickly and experience no long-term effects. This information may be useful to primary care providers counseling women about DCIS prior to screening mammography.

Category: Women's Health

Sphincter Preservation Therapy for Rectal Cancer

Candice Aitken, MD, Elizabeth Breen, MD, and Harvey J. Mamon, MD, PhD

Dr. Mamon is Clinical Director of the Department of Radiation Oncology at Brigham and Women's Hospital and the Dana-Farber Cancer Institute in Boston, MA. Dr. Aitken is Clinical Fellow at the Joint Center for Radiation Therapy and Dr. Breen is Colon and Rectal Surgeon in the Department of General and Gastrointestinal Surgery, both at the Harvard Medical School, in Boston, MA.

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Abstract

Rectal cancer presents a unique challenge to oncologists and patients due to the location and anatomy of the rectum and the difficulties inherent in pre-operative staging. These issues are especially important with distal rectal tumors when patients may face the decision of tumor control without sphincter preservation or more limited surgical procedures that may potentially compromise tumor control and thus survival. Current options for sphincter preservation for low-lying rectal tumors are preoperative radiotherapy with or without chemotherapy for tumor downstaging, local excision with or without adjuvant chemoradiation and low anterior resection with coloanal anastomosis. Pretreatment evaluation, by radiologic studies and pathologic predictors of lymph node involvement, is an integral part of determining which patients are suitable candidates for treatment with local excision. Preoperative chemoradiotherapy is a treatment option for some patients who are not initially considered to be candidates for sphincter preservation. Many investigators have suggested that the rate of sphincter preservation in patients with rectal cancer may be improved following preoperative chemotherapy and radiation. For properly selected patients, local excision holds promise as a means of achieving sphincter preservation.

Keywords

Rectal adenocarcinoma, local excision, sphincter preservation

Introduction

Rectal cancer presents a unique challenge to oncologists and patients due to the location and anatomy of the rectum and the difficulties inherent in preoperative staging. These issues are especially important with distal rectal tumors when patients may face the decision of tumor control without sphincter preservation (ie, abdominoperineal resection [APR]), or more limited surgical procedures that may potentially compromise tumor control and thus survival. APR is often necessary for tumor control, and for many years it has been the standard of care for distal rectal tumors that are not amenable to low anterior resection (LAR).

Quality of life (QOL) has been evaluated in patients who have been treated for rectal cancer.[1-3] APR is a relatively morbid procedure with a permanent colostomy, frequent genitourinary dysfunction, and male impotence. Preoperative and postoperative radiation therapy may also decrease QOL by their effects on sphincter function in patients who have undergone LAR with or without coloanal anastomosis.[1]

Current options for sphincter preservation for low-lying rectal tumors are preoperative radiotherapy with or without chemotherapy for tumor downstaging, local excision with or without adjuvant chemoradiation, and LAR with coloanal anastomosis. The selection of patients for these treatments depends on patient factors and the expertise of the treating physicians. In addition, limited data exist on whether local excision with or without adjuvant chemoradiotherapy compromises cancer control or cure rates.[4-7,13,16-29] APR may be necessary in certain patients with lymphovascular invasion, histologic grade, margin status, and other adverse pathologic features. Colostomy may be required in patients with poor anal sphincter function after LAR.

QOL After Treatment for Rectal Cancer

QOL after treatment for rectal cancer has been evaluated using a variety of methodologies in patients managed with a variety of treatment options and combinations. Virtually all suggest a detriment in QOL following surgery or combined modality therapy. Side effects may include sexual dysfunction, impotence, urinary dysfunction, altered body image following colostomy, and altered bowel habits in patients receiving a coloanal anastomosis.[1-3]

Williams et al[3] performed a retrospective review of 78 patients who underwent either an APR or sphincter-sparing surgery for tumors 5–12 cm from the anal verge. Patients who had undergone an APR had significantly more excess flatus, odor, change in body image, and higher depression scores than patients who had a sphincter-sparing procedure. These results may not apply to patients treated today given the changes in surgical technique and instrumentation since this study was published in 1983. In a more recent study by Grumann et al,[2] 73 patients treated with either LAR or APR were evaluated, and patients with APR had consistently higher QOL scores than those who had undergone an anterior resection.

Engel et al[1] recently reported the results of a 4-year prospective evaluation of patients who had undergone various surgical procedures for the treatment of rectal cancer. Three hundred twenty-nine patients returned QOL questionnaires, designed by the European Organization for Research and Treatment of Cancer: the Quality of Life Questionnaire (QLQ)-30 and the Colorectal Cancer-Specific QLQ (QLQ-CR38). These questionnaires were designed to assess QOL after rectal cancer treatment. Overall, patients who underwent anterior resection had better QOL scores than patients who had an APR. Patients who had a high anterior resection, for tumors located ≥8 cm from the anal verge, had the highest scores, followed by those patients who had low anterior resections, for tumors <8 cm from the anal verge, followed by those who underwent an APR. For those patients who returned multiple questionnaires over time, QOL scores improved with time for all variables except dyspnea and cognitive dysfunction.

Pretreatment Evaluation

For patients with distal rectal adenocarcinoma, most QOL measurements suggest a significant advantage to sphincter preservation, and local excision is thus preferable to APR for appropriately selected patients. Pretreatment evaluation is an integral part of determining which patients are suitable candidates for treatment with local excision. Most early retrospective studies of local excision have suggested that patients with T3 tumors are inappropriate candidates for this procedure due to an unacceptably high rate of local recurrence.[4-6] Preoperative staging is also important in selecting appropriate patients for neoadjuvant therapy, as chemotherapy and radiation are only indicated when there is evidence of T3 or node-positive disease. Thus, clinical determination of the T stage and N stage before beginning definitive therapy is an essential component of patient selection.

Historically, digital rectal examination (DRE) was the only method of determining tumor stage preoperatively. Patients whose tumors were fixed were more likely to have T4 disease, while those tumors that were mobile were more likely to be T3 or lower.[7] DRE has a reported accuracy of 44–83%.[7] The accuracy depends on the experience of the examiner and the length of the examining finger. It is not an effective means of determining lymph node involvement.

Endoscopic ultrasound (EUS) determines a stage of T3 or greater with accuracy from 67% to greater than 90%.[8] EUS is not as good at predicting T2 depth. The reported accuracy of EUS for determining T stage is 67–93%, with a sensitivity of 84% for T1, 76% for T2, 96% for T3, and 76% for T4.[9] One hypothesis of why EUS has difficulty with T2 tumors is that there may be a peri-tumoral inflammatory reaction that is difficult to distinguish by ultrasound (US). EUS is operator-dependent, influenced by the resolution of the US device, the depth of penetration of the US probe, the location of the tumor, and the degree of stenosis. For nodal staging, EUS relies on hypoechoic lymph nodes, a change in the shape of the lymph node or a decreased sonar attenuation coefficient. It has a reported accuracy for N stage of 62–83%.[8]

Computed tomography (CT) scan was initially thought to be very accurate in preoperative staging of rectal cancers. However, many of the early studies imaged patients with advanced disease. Due to the obliteration of fat planes between organs, CT images can readily detect T4 tumors. Overall accuracy for T stage is 33–77% and 22–73% for nodal staging. CT is more accurate for advanced stage and can accurately predict extension to other organs in 81% of cases versus 17% accuracy for detecting lymph nodes.[8] CT is less accurate than EUS or magnetic resonance imaging (MRI) in distinguishing among T1–T3 tumors and is not sensitive for detecting small lymph nodes.[8]

MRI using body, pelvic, and endorectal coils has been used to image rectal cancer patients. The body and pelvic coils have similar accuracy of 59–95% for T stage and 39–95% for nodal stage. The accuracy of MRI with an endorectal coil is 66–91%, and for nodal staging it is 72- Investigators at Brigham and Women's Hospital[10] used a combina pelvic phased array and endorectal coils in 64 consecutive rectal patients. Forty-one of these proceeded to surgery, and the patholog corresponded with the MRI stage in 36 of 41 patients (88%). By MRI accurately predicted 7 of 8 Tis/Stage 0 (88%), 15 of 17 stage I 2 of 3 stage II (66%), and 12 of 13 stage III patients (92%). G: et al[11] found similar sensitivity for determining the depth of pene through the bowel wall of 89% with a specificity of 80% and an ac of 86%. Their results for determining nodal stage were 67%, 71° 69% for sensitivity, specificity, and accuracy, respectively.

As other modalities, such as combination functional-anatomic ir (eg, positron emission tomography [PET]-CT), are developed, the allow for more accurate preoperative staging. MRI with lymph superparamagnetic nanoparticles was recently reported to have a accuracy in the detection of prostate cancer nodal metastases compared with nomograms or conventional MRI.[12]

Predictors of Lymph Node Involvement

Given the historical limitations of radiologic studies, investigator looked to pathologic predictors of lymph node involvement to dete selection criteria for patients who may be candidates for local ex Suitable candidates for local excision should have a low likelih involved lymph nodes.

Minsky et al[13] examined the pathologic predictors of lymph metastases in 168 patients with rectal adenocarcinoma treated at th England Deaconess Hospital between 1965 and 1978. On uni analysis, the incidence of lymph node metastases was correlatec the degree of tumor penetration of the bowel wall (T stage), the of differentiation, and the presence of colloid histology. For p: with T1, T2, T3, or T4 tumors, the risk of lymph node involv was 0%, 29%, 36%, and 53%, respectively (P=.04). For the of differentiation, 0% of well differentiated versus 30% of mod differentiated and 50% of poorly differentiated tumors demons lymph node involvement. Tumors with colloid (mucinous) his were more likely than tumors without colloid features to demo lymph node involvement (52% versus 30%, P=.04). Lymphatic va involvement demonstrated a trend toward increased risk of lymph involvement, but this did not reach statistical significance. Tum was not predictive of nodal metastases. On multivariate analysis, c histology, grade of the tumor, and depth of penetration of the bow were independent predictors of lymph node involvement. None 9 T1 tumors and none of the 7 well differentiated tumors demons nodal metastases regardless of other histopathologic features.

Brodsky et al[14] examined the pathologic features of 154 patient primary, pT1 or pT2, distal (as defined by a location <11 cm fro anal verge) adenocarcinomas of the rectum. Their overall rate of l node metastases was 20% (31 out of 154 patients). No corre was demonstrated between the size of the primary and the prese lymph node metastases; however, there were small numbers in size subcategory. Sessile, nonulcerated tumors were less likely to lymph node metastases than exophytic, ulcerated nonpolypoid l (11% versus 24%, P=.06). Depth of penetration of the bowel wa not significantly different when subclassifying T2 tumors by i middle, or outer muscular wall invasion. There was a trend to increased lymph node involvement in T2 versus T1 tumors versus 12%) but this did not reach statistical significance (P>.05) degree of differentiation was correlated with lymph node risk 0% of grade 1 (well differentiated) tumors versus 24% of grad

(moderately or poorly differentiated) tumors having positive lymph nodes (P=0.04). Colloid differentiation was not associated with lymph node risk. Lymphatic or blood vessel invasion (LVI) was significantly correlated with lymph node risk, with 17% lymph node involvement without lymphatic or blood vessel invasion versus 31% with LVI.

In a review of 353 patients with T1 sessile adenocarcinoma of the rectum treated with colonic resection, Nascimbeni et al[15] found lymph node metastases in 13% of patients. Predictors of lymph node involvement on univariate analysis were tumor size larger than 5 cm, Broder's histologic grade 3–4, lymphovascular invasion, and location in the distal third of the rectum. On multivariate analysis, invasion to the deepest third of the submucosa, lymphovascular invasion, and location in the distal third of the rectum remained predictive of lymph node involvement.

Sphincter Preservation

Local Excision

Local excision has been offered in limited circumstances to patients who refuse an APR or who are medically inoperable. Several retrospective, single institutional studies[6,13,14,16-18] and a meta-analysis by Graham[19] attempted to define a set of patients with a low risk of local recurrence and nodal metastases who would be candidates for local excision alone. Poorly differentiated histology, positive margins, and increasing depth of penetration of the bowel wall were associated with higher recurrence and mortality rates. There was a trend toward a tumor size greater than 3 cm being predictive of worse outcome. Selected series with results by T-stage are presented in Table 1. In an update of the experience from Memorial Sloan-Kettering Cancer Center (MSKCC), Paty et al[17] reported 10-year actuarial local recurrence rates of 17% and 28% for T1 and T2 tumors, respectively. The 10-year actuarial disease-specific survival rates were 74% and 75% for T1 and T2 tumors. Chakavarti et al[16] updated their series from Massachusetts General Hospital (MGH) and demonstrated a 5-year actuarial local control rate of 89% and 33% for T1 and T2 tumors treated with local excision without adjuvant radiation. In addition, they defined a subgroup of patients with high-risk features by the presence of lymphatic vessel invasion and/or poorly differentiated histology. The local control rates for the low-risk group as compared to the high-risk group was 97% versus 37%.

Table 1. Local Recurrence Rates for Patients Treated With Local Excision Without Adjuvant Radiation

MSKCC	33% (5/15)	14% (2/14)	50% (1/2)	25%	63%	>5 yr
Erlangen[6]	7% (4/54)	20% (4/20)	30% (3/10)	13%	64%	77.5 mo
MGH[3]	10% (2/20)	20% (1/5)	75% (3/4)	21%	0%	36 mo

MSKCC=Memorial Sloan-Kettering Cancer Center; MGH=Massachusetts General Hospital.

Table 2. Local Recurrence Rates for Patients Treated With Local Excision and Adjuvant Radiation

Florida[20]	89%*	75%*		86%	80%	65 mo
MGH[18]	10% (1/10)	18% (2/11)	33% (1/3)	15%	25%	26 mo
MSKCC[21]	0% (0/4)	17% (2/12)	33% (2/6)	18%	75%	37 mo

*Reported as actuarial rate of local control and 4/67 pts had chemotherapy.
MGH=Massachusetts General Hospital; MSKCC=Memorial Sloan-Kettering Cancer Center.

Several institutions[16-18,20,21] have reported retrospective reviews of their experience treating rectal adenocarcinoma with local excision with adjuvant radiation therapy, both with and without the use of chemotherapy (Table 2).

Based on the findings of the retrospective studies of local excision, criteria for patient selection were established and tested in several prospective studies. These trials are summarized in Table 3. MGH[22] began a prospective evaluation in 1985. Twenty patients were treated with local excision and postoperative radiation. After the first 5 patients, all patients received concurrent 5-fluorouracil (5-FU) chemotherapy for 3 days during the first and last week of radiotherapy (RT). In this series, there were no local recurrences, but 2 patients failed distantly.

Valentini et al[23] treated 21 patients with local excision followed by 44.6 Gy of adjuvant radiation therapy. None of the patients received chemotherapy concurrent with their radiation. Three patients failed locally; 1 of these 3 had a simultaneous lung metastasis and did not undergo salvage surgery. Of the 2 patients who underwent salvage APR, 1 developed a further local recurrence, for a salvage rate of 33%. None of the pathologic factors correlated with local recurrence by univariate or multivariate analysis.

Jessup et al[24] reported their results of 32 patients prospectively treated with sphincter preservation. Twenty-one of these patients were treated by local excision by either a transanal or transsacral approach. Patients with T1 tumors were observed, while those with T2 tumors were offered radiation with bolus or continuous infusion 5-FU chemotherapy, if they were younger than 70 years old. One of two patients with T3 disease underwent an immediate APR while the other received adjuvant 5-FU and radiation. At 25 months median follow-up, there were no local failures seen. The 2-year median follow-up limits the interpretation of these results, as Chakravarti et al[16] reported that in their series patients treated with adjuvant radiation tended to fail later than those who had not received adjuvant radiation, with a median time to recurrence of 55 months for those who received adjuvant therapy compared with 13.5 months for those who did not.

Fortunato et al[25] reported their experience with local excision at Fox Chase Cancer Center. Their series includes 16 patients entered on a phase I/II trial of 5 Gy preoperative radiation, followed by local excision and additional adjuvant RT. Also included in their analysis were 17 patients who either refused colostomy or were not candidates for a major surgical procedure. 15 patients received preoperative radiation and 20 patients received postoperative RT. The median postoperative dose was 50.4 Gy with a range of 27–63 Gy. Two patients received concurrent 5-FU with their adjuvant RT. One patient developed distant metastases while receiving adjuvant therapy. Four patients developed a local recurrence at a median time of 31.5 months. Three of these 4 patients were salvaged by APR, and 1 developed distant metastases 1 year after salvage anterior resection. This series is limited by the heterogeneity of the patient population, with half of the patients enrolled prospectively and subject to the eligibility criteria of the study while the other half of patients received local excision due to patient preference or medical comorbidities. The treatment regimen is also heterogeneous, with 15 patients receiving preoperative radiation and 20 patients receiving a range of doses of adjuvant radiation, only 2 of whom received concurrent 5-FU.

Researchers at M. D. Anderson Cancer Center (MDACC) studied 46 patients with rectal cancer treated with local excision and adjuvant radiation therapy. Eight of these patients received concurrent 5-FU chemotherapy. The tumors were located a median of 4.8 cm from the anal verge, with a median size of 3 cm. At a median follow-up of 36 months, 4 patients experienced a local failure, with 2 of these patients failing only

locally. An additional 4 patients failed distantly. Of interest is the finding that 7 of their 8 failures occurred within the first 24 months. This is in contrast to the findings of Chakravarti et al.[16] Whether this result would hold up with longer follow-up is unclear.

In the largest single institutional experience with local excision, Bleday et al[26] studied 48 patients with T1–T3 tumors that were smaller than 4 cm in diameter and had a proximal margin less than 10 cm from the anal verge. The surgery that was performed was a full-thickness local excision by a transanal, transsphincteric, or transcoccygeal approach with a goal of 1 cm margin around the tumor. Patients with T2 or T3 tumors received postoperative chemoradiation therapy with 5-FU given by bolus at 500 mg/m^2 on days 1–3 and 29–31 with 54 Gy. There were 3 operative complications (fistula). All of these 3 fistulae were seen in patients treated with either a transsphincteric or transcoccygeal approach. At a mean follow-up of 40.5 months, there was an 8% local recurrence rate (4 out of 48). Two of these local recurrences were in patients with T1 tumors, and the remaining 2 were in patients with T3 tumors. Three of 4 local recurrences were salvaged with an APR, but only 1 remained disease-free. Overall mortality was 6.2% (3 out of 48). Adverse pathologic features included the presence of LVI and positive final resection margins.

The Radiation Therapy Oncology Group (RTOG)[27] piloted a phase II trial of transanal full thickness local excision for the treatment of low-lying rectal cancers. The study opened in 1989 and closed when the Cancer and Leukemia Group B (CALGB) opened the successor trial. Sixty-five patients were eligible for the analysis. Patients were assigned to 3 treatment groups based on the pathology of the local excision specimen. If the tumor was a T1 tumor, smaller than 3 cm, without LVI, with at least 3 mm margins, and normal carcinoembryonic antigen (CEA) levels, patients were observed. The remaining patients were assigned to chemoradiation with 5-FU at 2 doses of radiation based on the final margin status. With a median follow-up of 6.1 years and a minimum follow-up of 5 years, the overall survival was 88% at 5 years. Eight patients required colostomy, 2 of which were temporary. Eleven patients (16%) developed a recurrence or progression of disease. The median time to recurrence was 24 months (range, 10–60 months). Three of these 11 patients failed only locally. In 5 patients whose first site of failure was local, salvage APR was performed. Four of these patients later developed distant metastases. There were trends for increased local recurrence rates with increased tumor extent as measured by increasing T stage or 21–40% circumferential bowel wall involvement.

Steele[28] and members of the CALGB explored full-thickness local excision in patients with small (≤4cm), distal rectal adenocarcinomas (proximal margin ≤10 cm from the anal verge). Patient eligibility was determined before registration and then again after local excision was performed. Patients with T1 tumors were observed, while patients with T2 and T3 tumors were treated with adjuvant chemoradiation. One hundred seventy-seven patients were accrued between October 1990 and October 1995. Fifty-one patients were ineligible after local excision, due in the majority of cases to either the inability to assess the final margin status, the lack of documentation of complete tumor excision, or the lack of pathologic documentation of a full thickness local excision. Twenty of these patients (39%) were ineligible due to unclear margins, 13 patients had tumors with T stage greater than T2, and 12 patients had tumors that were larger than 4 cm. An additional 10 patients were excluded due to less than a full thickness excision or margin information unavailability. Analysis of the entire group was not significantly different from the analysis that included only patients eligible for the protocol after local excision. With a median follow-up of 48 months, the 6-year survival and failure-free rates were 85% and 78%, respectively, for T1 and T2 tumors. There were 4 failures out of 59 T1 tumors and 10 failures out of 51 T2 tumors. Of the local-only failures in the T1 group (2 patients), 1 was salvaged with APR. For T2 tumors, there were 5 local-only failures, and 4 of these patients were successfully salvaged with APR.

From these prospective trials, it seems that selected, well differentiated, clinically staged T1 and T2 N0 tumors can be treated with local excision with or without adjuvant chemoradiotherapy. Factors that may be associated with higher local recurrence rates and thus warrant adjuvant treatment or more radical surgery include the presence of lymphovascular invasion, T2 tumors, less differentiated histology, less than a full thickness local excision, and positive microscopic margins.

Salvage After Failed Local Excision

Salvage rates after failed local excision vary widely among the reported series. Friel et al[29] describe 29 patients who underwent salvage surgery—17 APR, 10 LAR, 2 pelvic exenteration—after failed transanal local excision for a pT1 or pT2 rectal cancer. Only 2 patients received adjuvant RT after their local excision. The mean time to salvage surgery was 26 months (5–89 months). Twelve patients received preoperative radiotherapy before radical surgery. At a mean follow-up of 39 months (2–147 months), 17 patients (59%) were without evidence of disease. Six patients underwent noncurative surgeries. Eleven patients recurred after radical surgery (2 of whom had noncurative surgery). Six of these patients died of disease, and 5 are alive with recurrence.

Salvage rates from the CALGB trial[28] were reported by their initial T stage. Two patients with initial T1 disease had local recurrences without distant failure. Both underwent salvage APR; 1 of these patients died of rectal cancer, while the other is alive without evidence of recurrence. Of 7 patients with T2 disease who underwent salvage for local recurrence, 5 had local only recurrences. Four of 7 are alive without evidence of disease and the other 3 died of their disease.

Downstaging With Preoperative Chemoradiotherapy

Preoperative chemoradiotherapy is a treatment option for some patients who are not initially considered to be candidates for sphincter preservation. Two US trials randomizing patients to preoperative versus postoperative combined modality therapy closed early due to very poor accrual.[30,31]

Many different approaches to preoperative chemoradiation therapy have been studied in the treatment of rectal carcinomas (Table 4).[35-48] Many of these are preliminary studies with relatively short follow-up. Not all series report how many patients were initially candidates for sphincter preservation, making it difficult to assess the effect of preoperative therapy on the rates of sphincter preservation.

French investigators recently reported the preliminary results of the Lyon R96-02 trial of high dose preoperative radiation therapy with patients randomized to receive an endocavitary radiation boost dose of 85 Gy in 3 fractions.[32] Eighty-eight patients with ultrasound-staged T2–3 Nx adenocarcinoma were randomized. In the 45 patients randomized to receive an endocavitary boost, sphincter preservation was possible in 34 patients (76%) compared with 19 patients (44%) in the group that did not receive a boost (P=.0004). At 28 months median follow-up there was no significant difference in local control, survival, or postoperative complications with a 2-year overall survival (OS) of 90%. Seven patients in the boost group did not undergo surgery and were treated with an additional iridium boost of 25 Gy.

The German Colon Cancer Society[33] recently reported the preliminary results of a randomized trial comparing neoadjuvant chemoradiation therapy to postoperative chemoradiation in patients with clinically staged T3–4 or node-positive rectal adenocarcinomas. Eight hundred and twenty-three patients were randomized to preoperative chemoradiation with 5-FU and 50.4 Gy followed by surgery, or surgery followed by the same chemoradiation postoperatively. All patients received adjuvant

Table 3. Local Recurrence Rates From Prospective Trials of Local Excision Followed by Radiation Therapy

MGH[23]	20	47 mo	45 Gy pelvis 5–20 Gy boost	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Rome[23]	21	54 mo	44.6 Gy	None	1/9 11%	2/12 17%	—	14%	33%
JCRT[24]	21†	25 mo	45 Gy pelvis [illegible] Gy boost	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
FCCC[25]	23	56 mo	5 Gy Pre-op (n=15) 50.4 Gy median post-op (n=20)	2 pts	1/2 50%	2/15 13%	1/4 25%	4/21	75%
MDACC[4]	46	36 mo	45 Gy pelvis [illegible] Gy boost	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
NEDH[26]	48	40.5 mo	54 Gy for T2–3	5-FU	2/21	0/21	2/5	8%	25%
RTOG[27]	65	6 yr	45–50.4 Gy pelvis 5–20 Gy boost	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CALGB[28]	110	48 mo	54 Gy for T2	T2	3/59‖	7/51#	—	10/110	71% 5/7 (1/2 T1 4/5 T2)

* Two patients in this series failed distantly.
† Patients in the series who were treated with local excision.
‡The patient who did not receive chemotherapy subsequently underwent APR for T3 disease.
§ This patient failed locally and distantly.
‖ One of these 3 patients failed locally and distantly.
¶ Fourteen of these patients (those with margins >3 mm, without LVI, and with grade 1 or 2. tumors) did not receive adjuvant chemotherapy or radiation.
\# Two of these patients failed locally and distantly.
** All three of these patients failed locally and distantly.
†† There were 5 patients with local only failures.
RT=radiotherapy; MGH=Massachusetts General Hospital; JCRT=Joint Center for Radiation Therapy; FCCC=Fox Chase Cancer Center; MDACC=M. D. Anderson Cancer Center; NEDH=New England Deaconess Hospital; 5-FU=5-fluorouracil; RTOG=Radiation Therapy Oncology Group; CALGB=Cancer and Leukemia Group B; APR=abdominoperineal resection; LVI=lymphovascular invasion.

5-FU. At a median follow-up of 43 months, the 5-year pelvic recurrence rate was significantly lower in the neoadjuvant group, 7% versus 11% (P=.02). There was no difference in the rate of distant metastases. There was a nonsignificant trend toward improved disease-free survival (DFS) and OS in the preoperatively treated group with significantly less anastomotic stenosis. There was no difference in tolerance of the chemoradiation between preoperative and postoperative therapy. In the subgroup of patients with low-lying tumors, 39% in the preoperative group versus 19% in the postoperative group were able to undergo sphincter-preserving surgery. These are the only randomized data directly testing the hypothesis that neoadjuvant therapy can improve the rate of sphincter preservation, and the preliminary analysis suggests a doubling in the rate of sphincter preservation and a small but statistically significant improvement in local control, without a detriment in tolerability or overall survival.

Conclusions

Many investigators have suggested that the rate of sphincter preservation in patients with rectal cancer may be improved following preoperative chemotherapy and radiation. The results of the German Rectal Cancer Society study provide the first randomized data to support the hypothesis that neoadjuvant chemoradiation therapy increases the likelihood of sphincter-sparing surgery. This benefit was associated with a modest but statistically significant improvement in local control, while overall survival and toxicity were the same with preoperative or postoperative therapy. Other chemoradiation regimens currently under investigation may enhance the rate of sphincter preservation, and further study is warranted.

For properly selected patients, local excision holds promise as a means of achieving sphincter preservation. It is highly unlikely that a study will ever be conducted randomizing patients to local excision versus

Table 4. SP Rates After Treatment With Preoperative Chemoradiation in Locally Advanced Rectal Cancer

MSKCC[36]	45 Gy pelvis 5.4 Gy boost	5-FU/LV	72	47/68 (69%)	31/35 thought to require APR underwent SSS
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
University of Kentucky[38]	45 Gy pelvis 5-15 Gy boost	Bolus or CI 5-FU	77	49/77 (64%)	Fixed, tethered, T4 or recurrent tumors
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hospital Saint-Andre, France[40]	44 Gy pelvis 0-10 Gy boost	Bolus or CI 5-FU	118	43/60 (72)	Subset of patients with tumors <6 cm from anal verge
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
France[42]	45 Gy pelvis	5-FU/LV	66	35/60 (58%)	ultrasound T3 or tethered
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Sweden[44]	45 Gy pelvis 5.4 Gy boost	Irinotecan and 5-FU	32	16/32 (50%)	7/9 thought to require APR had SSS
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Lyon, France[46]	45 Gy pelvis 5.4 Gy boost	Oxaliplatin, 5-FU/LV	40	25/40 (63%)	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Spain[48]	45 Gy pelvis 5.4 Gy boost	LV, UFT	41	26/41 (63%)	10 pts thought to require APR underwent SSS

SP=sphincter preservation; RT=radiotherapy; MSKCC=Memorial Sloan-Kettering Cancer Center; 5-FU=5-fluorouracil; LV=leucovorin; APR=abdominoperineal resection; SSS=sphincter-sparing surgery; CI=continuous infusion; MDACC=M. D. Anderson Cancer Center; CMT=combined modality therapy; UFT=tegafur, uracil, 5-FU.

APR; we are thus limited in our ability to determine the relative efficacy of the 2 surgical approaches. A significant body of retrospective and phase II prospective data, however, suggests that patients with small distal T1 tumors and no adverse histological features do well with local excision. These same studies suggest that local excision and adjuvant chemoradiation are appropriate for patients with T2 tumors or T1 tumors with unfavorable histology. Whether T2 tumors with adverse features may be managed with local excision remains controversial and will likely be clarified as further studies are conducted.

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Ability of Preoperative Endorectal Magnetic Resonance Imaging to Identify Extracapsular Extension and Seminal Vesicle Invasion in a Screened Population

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Purpose: To evaluate the ability of endorectal magnetic resonance imaging (erMRI) to identify extracapsular extension and seminal vesicle invasion in men screened for prostate cancer using serial prostate-specific antigen (PSA) testing.

Materials and Methods: Seventy-three patients with clinical tumor category T1c or T2 adenocarcinoma of the prostate underwent pre-operative erMRI followed by radical prostatectomy at the Brigham and Women's Hospital between 1998 and 2004. Patient characteristics are shown in table 1. A single expert genitourinary radiologist read the endorectal MRI. Patients were classified as low risk (PSA < 10 ng/ml and biopsy Gleason score 6 or less and clinical category T1c or T2a) versus all others. A correct prediction for erMRI required that the both the laterality and presence of extracapsular extension (ECE) and/or seminal vesicle invasion (SVI) needed to be concordant between the erMRI and final pathology.

Results: Of the 33 patients with Gleason 7 disease or higher 81.8% (27/33) had a PSA < 10 ng/ml and 63.6% (21/33) were clinical category T1c. There were 11 (15.3%) patients with ECE and 2 (2.7%) with SVI. For the low risk patients, the positive and negative predictive value for ECE was 9.1% (1/11) and 96.8% (61/63) respectively and for SVI these values were 0% (0/1) and 100% (73/73) respectively. In the remaining patients these values were 14.3% (1/7) and 83.1% (54/65) for ECE and undefined (0/0) and 95.8% (69/72) for SVI respectively.

Conclusion: The negative predictive value of erMRI is high (> 83%) for patients with screen detected prostate cancer independent of the risk group; however the positive predictive value is low. The low positive predictive value may be explained by the shift toward smaller tumor volumes despite high-grade disease in a population diagnosed during using PSA screening.

Patient Characteristics

		Biopsy Gleason		
		6 or less N=40	7 N=29	8-10 N=4
2003 AJCC T Stage	T1a/T1b	1	0	0
	T1c	33	20	1
	T2a	6	7	2
	T2b	0	2	0
	T2c	0	0	1
PSA ng/dL	0-4.0	13	5	1
	>4-10.0	24	19	2
	>10.0-20	3	5	1

	>20	0	0	0

Adolescent Diet and Incidence of Proliferative Benign Breast Disease

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Abstract

Studies of adult diet and risk of breast cancer have yielded mainly null results, but this does not rule out a possible impact of adolescent diet. This study examined associations between components of adolescent diet and risk of proliferative benign breast disease (BBD), a marker for breast cancer. The study population consisted of 29,494 women in the Nurses' Health Study II who completed a questionnaire on adolescent diet in 1998 and who were 33–53 years of age at that time. A total of 470 new cases of proliferative BBD were identified between 1991 and 1997. Incidence rate ratios (RRs) and 95% confidence intervals (CIs) were calculated for quartiles of energy-adjusted intakes, using the lowest quartile of each as the reference group. Total fat intake during adolescence was unrelated to risk of proliferative BBD, although there were positive associations for intakes of animal fat and monounsaturated fat and an inverse association for intake of vegetable fat. For vitamin E intake, the multivariate RRs were 1.13, 0.88, and 0.79 (95% CI, 0.61–1.04) for women in the second, third, and highest quartiles, respectively (*P* for trend = 0.05). The multivariate RRs were 0.94, 0.99, and 0.75 (95% CI, 0.57–0.98) for women in increasing quartiles of fiber intake (*P* for trend = 0.05). Vegetable fat, vitamin E, and fiber intakes during adolescence were inversely associated with risk of proliferative BBD in this population. Confirmation of these associations may suggest a means for prevention of breast cancer.

Introduction

BBD[5] is a heterogeneous group of lesions including a variety of tissue abnormalities. Certain subtypes of BBD are associated with increased breast cancer risk. Compared with women with nonproliferative lesions, women whose biopsies show proliferative changes without atypia have a 1.5–2-fold greater risk of developing breast cancer in the future, and women with atypical hyperplasia have a 3.5–5-fold greater risk (1). These findings suggest that proliferative BBD may be a marker for breast cancer.

The relation of diet to breast cancer risk has been investigated in numerous epidemiological studies. Although ecologic studies and some case-control studies originally suggested that adult intakes of total and saturated fat might be positively associated with breast cancer risk (2, 3), more recent prospective studies have not supported these earlier findings (4–6). Carotenoids and vitamins C and E have antioxidant properties that may contribute to reduced breast cancer risk (7, 8), and vitamin A also may confer some protection by regulating cell differentiation (9, 10). Results from epidemiological studies of these micronutrients have been inconclusive (2), although a recent prospective study showed decreasing risk of breast cancer with increasing serum carotenoid levels (11). Similarly, studies of adult diet and BBD have not identified any clear and consistent associations (12–15).

The lack of evidence supporting the role of adult diet in relation to risk of breast cancer does not rule out a possible impact of childhood and adolescent diet. Reviewing the epidemiological evidence on the potential role of early life factors, Colditz and Frazier (16) concluded that exposures between menarche and first birth may exert important effects on future risk. Furthermore, studies of mammary gland development in rats have shown that breast tissue may be most vulnerable to carcinogens during this time period due to rapid proliferation of cells and lack of terminal differentiation (17). Hence, previous studies may have focused on the wrong time period, because adolescent diet may have a stronger influence on risk than adult diet.

To date, only a few studies have examined the role of adolescent diet in the etiology of breast cancer (18–21). In a population-based case-control study that included 172 cases and 190 controls, a nonsignificant inverse association between adolescent fat intake and premenopausal breast cancer risk was seen (19). Total fiber intake during adolescence was associated with increased breast cancer risk in postmenopausal women (odds ratio for highest *versus* lowest quartile, 6.6; 95% CI, 1.5–29.6), but fiber from grains was associated with decreased risk in both premenopausal and postmenopausal women. In a larger population-based case-control study including 1647 incident breast cancer cases and 1501 controls, there was a nonsignificant inverse association between fruit and vegetable consumption during adolescence and breast cancer risk (odds ratio for highest *versus* lowest quartile, 0.9; 95% CI, 0.7–1.1), whereas adolescent intakes of animal fat, high-fat foods, high-fat snacks and desserts, and dairy products had no clear relation to risk (20). Neither of these studies examined associations between intakes of specific micronutrients during adolescence and breast cancer risk. In a recent retrospective analysis in the

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[5] The abbreviations used are: BBD, benign breast disease; FFQ, food frequency questionnaire; RR, rate ratio; CI, confidence interval.

Nurses' Health Study that included 843 incident cases of breast cancer, higher consumption of eggs, vegetable fat, and fiber during adolescence were associated with decreased breast cancer risk (21). The 24-item FFQ used in this study, however, did not allow complete assessment of total energy intake or specific nutrients, due to the restricted list of foods.

If dietary factors are involved in the early stages of breast cancer development, important associations may exist between components of adolescent diet and marker lesions such as BBD. To examine this hypothesis, we studied intakes of total fat and specific types of fat, micronutrients, fiber, and foods during adolescence in relation to risk of proliferative BBD within the Nurses' Health Study II.

Materials and Methods

Study Design and Population. The Nurses' Health Study II is a prospective cohort study that began in 1989, when 116,671 female nurses between the ages of 25 and 44 years completed a mailed, self-administered questionnaire including information on a variety of health behaviors and conditions. Since 1989, questionnaires have been sent to these women every 2 years to obtain updated information on lifestyle factors and recent medical events. The response rate during each 2-year period has been ≥90%.

The present study was a retrospective analysis within the Nurses' Health Study II. The study population included 45,947 women who completed a questionnaire on adolescent diet (described below) in 1998 and had plausible values for total energy intake (between 600 and 5000 kcal/day). We excluded 16,057 women who had a self-reported or histologically confirmed diagnosis of BBD before return of the 1991 questionnaire because pathology specimens were only collected for incident cases diagnosed after the 1991 cycle. A total of 396 women were excluded because of a prior diagnosis of cancer other than non-melanoma skin cancer. The final study population consisted of 29,494 women. This investigation was approved by human research committees at the Harvard School of Public Health and Brigham and Women's Hospital.

Adolescent Diet Questionnaire. In 1998, a semiquantitative FFQ with 131 items on adolescent diet was completed by 45,947 women who had previously indicated that they would be willing to participate. This self-administered questionnaire was a modified version of the validated FFQ used to assess adult diet in the Nurses' Health Study and several other cohorts. Participants were asked to report how often they consumed a specified quantity of 122 foods and beverages during high school, further defined as ages 13–18 years.

A reproducibility study conducted among a random sample of women in a separate cohort showed moderately high correlations between two separate recalls, 8 years apart, of consumption of 24 food items during high school (22). The average Spearman correlation coefficient for the first and second recall was 0.57, although values ranged from 0.38 to 0.74. The mean correlation between reported high school diet and current diet was only 0.25, which may indicate that current diet did not strongly affect recall of remote diet. Although data on the validity of the adolescent diet questionnaire are not yet available, research in survey methodology shows that provision of a clear definition of the reference time period (high school, in this case) enhances recall on self-administered questionnaires (23).

Energy, fat, and micronutrient intakes were derived from participants' responses on the FFQ using an extensive food composition database maintained by a team of research dietitians. Because the composition of some foods has changed over time, food composition data from the relevant time period (1960s and 1970s) were used, when available, to provide the best approximation of intakes during adolescence.

Identification of Cases of BBD. On the 1989 baseline questionnaire, all women were asked if they had ever received a diagnosis of fibrocystic or other BBD from a physician. On each of the subsequent biennial questionnaires in 1991, 1993, 1995, and 1997, women were asked if they had received a diagnosis of BBD since the previous questionnaire and if the diagnosis had been confirmed by biopsy and/or aspiration. A total of 2,454 participants reported a first diagnosis of biopsy-confirmed BBD between 1991 and 1997. Of these cases, 1,022 (42%) contributed information on diet during adolescence. This is similar to the overall proportion of women in the entire Nurses' Health Study II cohort with adolescent dietary data [45,947 of 116,671 (39%)].

Because proliferative BBD, in contrast with other subtypes, is associated with increased risk of breast cancer, proliferative BBD with or without atypia was the primary outcome of interest. Women who reported a first diagnosis of biopsy-confirmed BBD on the 1993, 1995, or 1997 questionnaires were contacted to confirm the diagnosis and to acquire permission to review their pathology specimens. Among the 987 women with adolescent diet information who were initially contacted, 89% (883) confirmed the BBD diagnosis and granted permission for review of their biopsy records and pathology slides. Adequate pathology material was obtained and reviewed for 800 women (91% of those who had given their permission); 754 (94%) of these were confirmed to be eligible cases, and a valid diagnosis was obtained. The main reasons for exclusion were that the pathology specimen did not contain breast tissue or that the biopsy date was before June 1991. Women were also excluded if their biopsy date was after the date they reported BBD or if they had a prior cancer, a diagnosis of breast cancer within the same questionnaire cycle, or a diagnosis of breast carcinoma *in situ*. Included cases were slightly older and reported greater alcohol consumption between ages 18 and 22 years than cases not included in the analysis, but included and excluded cases were similar in terms of other characteristics (data not shown).

Biopsy materials were reviewed by one of four pathologists (S. J. Schnitt, J. L. Connolly, T. W. Jacobs, or G. Peiro) who had no knowledge of participants' exposure information. All slides from the breast biopsies were classified as normal or nonproliferative, proliferative without atypia, or atypical hyperplasia, according to the criteria of Dupont and Page (24). Any biopsies that showed atypia or questionable atypia were jointly reviewed by two pathologists (S. J. Schnitt and J. L. Connolly) with one of the other pathologists (T. W. Jacobs or G. Peiro) and a consensus diagnosis was reached. Biopsy tissue with intraductal papilloma, radial scar, sclerosing adenosis, fibroadenoma, fibroadenomatous change, or moderate to florid ductal hyperplasia in the absence of atypical hyperplasia was classified as proliferative without atypia.

Of the 754 cases identified among eligible participants, 470 (62%) were classified as proliferative (with or without atypia) by the study pathologists. Because there were only 39 cases of atypical hyperplasia, this was not examined as a separate outcome in the main analyses. Consistent with a previous report from this cohort, proliferative cases were less likely to report a family history of breast cancer and more likely to have had menarche before age 12 years compared with nonproliferative cases (25).

Statistical Analysis. Cohort analyses were conducted among the 29,494 women who completed the adolescent diet questionnaire and met the other eligibility criteria, using proliferative disease with or without atypia as the primary outcome. Secondary analyses were also performed using all self-reported BBD and self-reported BBD confirmed by biopsy as outcomes. Eligible participants contributed person-time of follow-up from the time they returned the 1991 questionnaire until the return date of the 1997 questionnaire, death from any cause, report of BBD or cancer other than non-melanoma skin cancer, or loss to follow-up. This method allows for the updating of time-varying covariates every 2 years.

Total fat, types of fat, and specific micronutrients were the main exposures of interest. To adjust for total energy intake (26), total fat and types of fat were examined as nutrient densities, computed as percentages of total caloric intake. For micronutrients, energy-adjusted intakes were calculated using the residual method, in which energy-adjusted values are the residuals from a regression model with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable (26). Fat densities and energy-adjusted micronutrient residuals were then divided into quartiles based on the distributions of values for all women who completed the adolescent diet questionnaire.

Age-adjusted incidence RRs for proliferative BBD were calculated for quartiles of energy-adjusted fat and micronutrient intakes, using the lowest quartile of each as the reference group, and two-sided tests for trend were also conducted. Cox proportional hazards regression was used to estimate RRs and 95% CIs for quartiles of fat and micronutrient intakes while controlling for relevant covariates simultaneously. The multivariate Cox models adjusted for the following variables: age in months, time period (three periods), age at menarche (<12, 12, 13, or ≥14 years), menopausal status (premenopausal, postmenopausal, or uncertain), body mass index at age 18 years (<19, 19–20.4, 20.5–21.9, 22–24.9, ≥25 kg/m^2), history of breast cancer in mother or sister (yes/no), alcohol intake between ages 18 and 22 years (0, <5, 5–14, ≥15 g/day), and multivitamin use between ages 13 and 18 years (yes/no). These variables were selected based on their established or hypothesized associations with breast cancer, BBD, or adolescent diet. Terms for quartiles of total energy intake were also included in multivariate models to adjust fully for potential confounding, and types of fat were also mutually adjusted for one another.

Further analyses of associations between individual foods and proliferative BBD were also conducted. The original frequency categories for a serving of each food (ranging from "never or less than once per month" to "6 or more per day") were used first, and then categories with small numbers of participants were combined to improve the stability of the estimates. Foods were selected according to their contributions to macro- and micronutrients that appeared most important in the previous set of analyses. In addition, three major food groups (fruits and vegetables, meats, and dairy foods) were examined in relation to risk of proliferative BBD. Categories for servings of these food groups were determined based on their distributions among women who completed the adolescent diet questionnaire, and total energy intake was included in the multivariate models.

Results

Between 1991 and 1997, 29,494 women in the study contributed 165,141 person-years of follow-up. The baseline distributions of selected characteristics of participants are presented in Table 1, according to their intakes of fat and vitamins A, E, and C during adolescence. Age, family history of breast cancer, age at menarche, menopausal status, alcohol intake between ages 18 and 22, and body mass index at age 18 did not vary substantially across quartiles of intake.

We observed no association between total fat intake during adolescence and incidence of proliferative BBD (Table 2). There was some suggestion of a positive association for animal fat intake and an inverse association for vegetable fat intake, however. Compared with women in the lowest quartile of animal fat intake, the multivariate RRs for proliferative BBD were 1.24 (95% CI, 0.94–1.63) for women in the second quartile, 1.16 (95% CI, 0.87–1.54) for women in the third quartile, and 1.33 (95% CI, 1.00–1.78) for women in the highest quartile (*P* for trend = 0.08). For vegetable fat intake, the multivariate RRs were 0.89 (95% CI, 0.70–1.14), 0.92 (95% CI, 0.71–1.18), and 0.73 (95% CI, 0.55–0.96) for women in the second, third, and highest quartiles, respectively (*P* for trend = 0.04). Because animal fat and vegetable fat intake are negatively correlated, we also included both animal fat and vegetable fat in the same multivariate model to mutually adjust for one another. Although the RRs were somewhat attenuated and the trends were no longer statistically significant, the directions of both associations remained the same.

Table 1 Age-standardized percentages and means for characteristics of participants according to fat and vitamin intake during adolescence[a]

	Total fat quartile[b]		Total vitamin A quartile[c]		Total vitamin E quartile[c]		Total vitamin C quartile[c]	
	1 (low)	4 (high)	1 (low)	4 (high)	1 (low)	4 (high)	1 (low)	4 (high)
No. of women	7658	7140	7474	7313	7340	7519	7358	7371
Percentage of group								
Family history of breast cancer in mother or sister(s)	8	9	8	8	8	9	8	9
Age at menarche < 12 yrs	25	25	24	25	23	26	24	25
Premenopausal in 1991	98	98	98	98	98	98	98	98
Mean								
Age in 1991 (yrs)	34	37	35	36	37	35	36	35
Alcohol intake between ages 18 and 22 (g/day)	5	6	6	5	5	6	5	5
BMI at age 18 (kg/m^2)	21	22	21	21	21	22	22	21
Adolescent fat intake (% of energy)	35	46	42	39	40	42	43	38
Adolescent fiber intake (g/day, energy-adjusted)	25	18	18	25	19	23	18	25

[a] Except for the data on mean age, all data shown are standardized to the age distribution of the cohort in 1991.
[b] Quartile of percent calories from fat.
[c] Quartile of energy-adjusted nutrient residuals.

Table 2 RRs and 95% CIs of proliferative BBD among 29,494 women followed from 1991 to 1997, according to percentage of calories from total fat and types of fat during adolescence

	Quartile of percentage of calories from fat				P for trend
	1 (low)	2	3	4 (high)	
Total fat					
Intake (% of energy)[a]	35.6	39.4	42.1	45.5	
Cases of BBD[b]	106	122	109	133	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.15 (0.89–1.49)	1.01 (0.77–1.33)	1.24 (0.95–1.61)	0.22
Multivariate[c]	1.00 (referent)	1.10 (0.85–1.43)	0.98 (0.75–1.29)	1.17 (0.90–1.52)	0.37
Animal fat					
Intake (% of energy)[a]	19.5	24.0	27.6	32.4	
Cases of BBD[b]	94	121	119	136	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.26 (0.96–1.67)	1.24 (0.92–1.67)	1.55 (1.15–2.09)	0.03
Multivariate[c]	1.00 (referent)	1.24 (0.94–1.63)	1.16 (0.87–1.54)	1.33 (1.00–1.78)	0.08
Additional adjustment for vegetable fat	1.00 (referent)	1.18 (0.89–1.57)	1.07 (0.79–1.45)	1.19 (0.86–1.65)	0.40
Vegetable fat					
Intake (% of energy)[a]	10.2	13.3	15.8	19.3	
Cases of BBD[b]	136	120	121	93	
RR (95% CI)					
Age-adjusted	1.00 (referent)	0.88 (0.69–1.13)	0.94 (0.74–1.21)	0.69 (0.52–0.92)	0.02
Multivariate[c]	1.00 (referent)	0.89 (0.70–1.14)	0.92 (0.71–1.18)	0.73 (0.55–0.96)	0.04
Additional adjustment for animal fat	1.00 (referent)	0.91 (0.70–1.18)	0.95 (0.72–1.25)	0.77 (0.56–1.06)	0.15
Saturated fat					
Intake (% of energy)[a]	13.3	15.2	16.8	18.9	
Cases of BBD[b]	100	121	118	131	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.23 (0.94–1.60)	1.12 (0.85–1.49)	1.30 (0.98–1.72)	0.12
Multivariate[c]	1.00 (referent)	1.15 (0.88–1.51)	1.09 (0.83–1.44)	1.19 (0.90–1.56)	0.30
Additional adjustment for monounsaturated, polyunsaturated, and trans-unsaturated fats	1.00 (referent)	1.02 (0.76–1.37)	0.88 (0.63–1.23)	0.87 (0.59–1.27)	0.36
Monounsaturated fat					
Intake (% of energy)[a]	12.6	14.1	15.1	16.5	
Cases of BBD[b]	101	117	120	132	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.18 (0.90–1.54)	1.23 (0.94–1.60)	1.32 (1.01–1.72)	0.04
Multivariate[c]	1.00 (referent)	1.15 (0.88–1.50)	1.19 (0.91–1.56)	1.28 (0.99–1.67)	0.06
Additional adjustment for saturated, polyunsaturated, and trans-unsaturated fats	1.00 (referent)	1.21 (0.90–1.64)	1.33 (0.95–1.85)	1.52 (1.05–2.21)	0.03
Polyunsaturated fat					
Intake (% of energy)[a]	5.2	6.1	6.9	8.1	
Cases of BBD[b]	124	121	126	99	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.02 (0.79–1.30)	1.04 (0.81–1.34)	0.81 (0.62–1.06)	0.22
Multivariate[c]	1.00 (referent)	1.00 (0.78–1.29)	1.07 (0.83–1.38)	0.81 (0.62–1.06)	0.17
Additional adjustment for saturated, monounsaturated, and trans-unsaturated fats	1.00 (referent)	0.97 (0.75–1.25)	1.00 (0.77–1.31)	0.74 (0.55–1.00)	0.06
Trans-unsaturated fat					
Intake (% of energy)[a]	1.6	2.0	2.5	3.2	
Cases of BBD[b]	115	128	126	101	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.17 (0.90–1.50)	1.13 (0.87–1.47)	0.89 (0.67–1.67)	0.48
Multivariate[c]	1.00 (referent)	1.18 (0.91–1.52)	1.16 (0.90–1.51)	0.92 (0.70–1.21)	0.39
Additional adjustment for saturated, monounsaturated, and polyunsaturated fats	1.00 (referent)	1.17 (0.90–1.51)	1.14 (0.87–1.50)	0.91 (0.68–1.21)	0.33

[a] Values for % of energy are medians of each quartile.
[b] A total of 470 cases of proliferative BBD (with or without atypia) were diagnosed during the follow-up period.
[c] The multivariate models are adjusted for the following: age in months, time period (3 periods), total energy intake (quartiles), age at menarche (<12, 12, 13, or ≥14 years), menopausal status (premenopausal, postmenopausal, or uncertain), body mass index at age 18 (<19, 19–20.4, 20.5–21.9, 22–24.9, or ≥25 kg/m²), history of breast cancer in mother or sister (yes/no), alcohol intake between ages 18 and 22 (0, <5, 5–14, or ≥15 g/day), and multivitamin use between ages 13 and 18 (yes/no).

In addition, monounsaturated fat was positively associated with risk of proliferative BBD. The multivariate RRs were 1.21 (95% CI, 0.90–1.64), 1.33 (95% CI, 0.95–1.85), and 1.52 (95% CI, 1.05–2.21) for women in the second, third, and fourth quartiles of monounsaturated fat intake, respectively, after adjustment for other types of fat (*P* for trend = 0.03). Polyunsaturated fat intake showed a nonsignificant inverse association with risk, whereas saturated fat and trans-unsaturated fat intakes were unrelated to risk.

Of the micronutrients that were examined, only vitamin E

and total vitamin A intakes were inversely associated with risk of proliferative BBD (Table 3). Intakes of vitamin C, retinol, carotenoids, and folate were not related to risk. The weak inverse association for vitamin E was most apparent in the two quartiles with highest intake. Compared with women in the lowest quartile of vitamin E intake, the multivariate RRs for proliferative BBD were 0.88 (95% CI, 0.68–1.14) for women in the third quartile and 0.79 (95% CI, 0.61–1.04) for women in the highest quartile (P for trend = 0.05). The inverse association for vitamin A was slightly weaker, and the trend was nonsignificant. The multivariate RR was 0.84 (95% CI, 0.64–1.11) for women in the highest *versus* the lowest quartile of total vitamin A intake (P for trend = 0.07). These associations were still apparent when only vitamins from food sources, as opposed to supplements, were included.

Because vegetable fat was inversely associated with risk of proliferative BBD, and vegetable fat is a major source of dietary vitamin E, we included both vitamin E and vegetable fat in the same multivariate model. The inverse association for vegetable fat was somewhat attenuated after adjustment for animal fat and vitamin E; the RR for women in the highest quartile *versus* the lowest quartile was 0.87 (95% CI, 0.59–1.28; P for trend = 0.59). The inverse association for vitamin E was also attenuated after adjustment for vegetable fat, with a RR of 0.88 (95% CI, 0.63–1.22; P for trend = 0.38) for women in the highest quartile *versus* the lowest quartile. The directions of both associations, however, remained the same.

In addition, we observed a significant inverse association between fiber intake and proliferative BBD (Table 4). The multivariate RR was 0.75 (95% CI, 0.57–0.98) for women in the highest *versus* the lowest quartile of fiber intake (P for trend = 0.05). Neither fruit nor vegetable intake, separately or combined, was significantly associated with risk of proliferative BBD.

Both total meat intake and red meat intake were positively associated with risk of proliferative BBD (data not shown). For total meat intake, the multivariate RR for women who ate 3 or more servings/day compared with those who ate less than 1.5 servings/day was 1.50 (95% CI, 1.01–2.22; P for trend = 0.03), whereas for red meat intake, the multivariate RR for women who ate 2 or more servings/day compared with those who ate less than 1 serving/day was 1.33 (95% CI, 0.97–1.84; P for trend = 0.03). These RRs were somewhat attenuated after adjustment for animal fat, but the directions of both associations remained unchanged. No associations were observed for intakes of milk or total, high-fat, or low-fat dairy foods.

We also calculated age-adjusted and multivariate ratios for associations between intakes of individual foods and proliferative BBD. We examined foods that contributed substantially to intakes of animal fat, vegetable fat, vitamin E, vitamin A, and fiber during adolescence. Consumption of nuts and raw carrots were inversely associated with risk of proliferative BBD. For nuts, the multivariate RRs for women who ate 2–3 servings/month, 1 serving/week, and >1 serving/week were 1.03 (95% CI, 0.82–1.29), 0.93 (95% CI, 0.73–1.18), and 0.64 (95% CI, 0.45–0.91), respectively, compared with women who ate 1 serving/month or less (P for trend = 0.02). The multivariate RRs for intake of raw carrots were 0.87 (95% CI, 0.68–1.11) for women who ate 1–3 servings/month, 0.74 (95% CI, 0.57–0.96) for women who ate 1 serving/week, and 0.70 (95% CI, 0.52–0.92) for women who ate ≥2 servings/week, compared with those who ate <1 serving/month (P for trend = 0.02). This inverse association was not observed for intake of cooked carrots. Nonsignificant inverse associations were also observed for intakes of grapes, strawberries, oranges, and fruit juice. Consumption of hot dogs was positively associated with risk of proliferative BBD; multivariate RRs for women who ate 1–3 servings/month, 1 serving/week, and ≥2 servings/week were 1.02 (95% CI, 0.76–1.38), 1.11 (95% CI, 0.81–1.50), and 1.49 (95% CI, 1.04–2.13), respectively (P for trend = 0.01). This association remained significant even after adjustment for animal fat. There were also nonsignificant positive associations between intakes of processed meats (*e.g.*, cold cuts), bacon, and pork and proliferative BBD.

Finally, in the secondary analyses using all self-reported BBD as the outcome (5012 cases), we observed no consistent associations for intakes of total fat or any types of fat. Restricting the outcome to cases that participants reported as confirmed by biopsy (998 cases), we observed a weak inverse association for vegetable fat intake; however, the trend was not statistically significant (P = 0.18) and was no longer apparent after adjustment for vitamin E. Animal fat intake was not associated with risk of biopsy-confirmed BBD. There was a nonsignificant positive association for monounsaturated fat intake, whereas saturated, polyunsaturated, and trans-unsaturated fat intakes were unrelated to risk. There were significant inverse associations for intakes of vitamin C, vitamin E, vitamin A, β-cryptoxanthin, fiber, and fruits and self-reported BBD; however, the actual risk reduction in the highest quartile of each of these was small, approximately 10% or less. For self-reported BBD confirmed by biopsy, some of the same inverse associations were apparent, but the inverse association for vitamin E was the only one that was statistically significant; the multivariate RRs were 0.94 (95% CI, 0.79–1.11), 0.88 (95% CI, 0.74–1.05), and 0.84 (95% CI, 0.70–1.00) for women in increasing quartiles of vitamin E intake (P for trend = 0.04).

Discussion

In this study, we observed that vitamin E and fiber intake during adolescence were inversely related to the incidence of proliferative BBD. Women in the highest quartiles of vitamin E and fiber intake had approximately 20% and 25% lower risk of proliferative BBD compared with women in the lowest quartiles, respectively. Polyunsaturated fat and vegetable fat intake (which are highly correlated with each other) were also inversely associated with risk of proliferative BBD. However, the associations between vitamin E and vegetable fat in relation to proliferative BBD were greatly attenuated after mutual adjustment for one another, making it difficult to determine which factor is responsible for the observed inverse associations. Monounsaturated fat intake during adolescence (derived mainly from animal sources such as beef, milk, and pork in this population) was positively associated with risk of proliferative BBD, whereas total fat, saturated fat, and trans-unsaturated fat intakes were unrelated to risk. The patterns for vitamin E, vegetable fat, monounsaturated fat, and fiber were still apparent when the study population was restricted to participants who reported having a mammogram or clinical breast exam within the previous 2 years (data not shown), suggesting that selective referral for biopsy and subsequent diagnosis of BBD based on adolescent diet is not a viable explanation for these results.

An important limitation of this study is the retrospective assessment of adolescent diet and the potential for recall bias: a diagnosis of BBD between 1991 and 1997 could have influenced participants' recall or reporting of adolescent diet in 1998. If women diagnosed with BBD systematically over- or under-reported their consumption of certain foods during adolescence in comparison with women who did not develop BBD, this could bias our results. A nested case-control study in a

Table 3 RRs and 95% CIs of proliferative BBD among 29,494 women followed from 1991 to 1997, according to energy-adjusted micronutrient intakes during adolescence

	Quartile of energy-adjusted micronutrient intake				*P* for trend
	1 (low)	2	3	4 (high)	
Vitamin C (including supplements)					
Intake (mg/day)[a]	81	120	158	228	
Cases of BBD[b]	126	131	104	109	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.03 (0.81–1.32)	0.81 (0.53–1.05)	0.87 (0.67–1.12)	0.11
Multivariate[c]	1.00 (referent)	1.05 (0.82–1.34)	0.82 (0.63–1.07)	0.90 (0.68–1.18)	0.24
Vitamin E (including supplements)					
Intake (mg/day)[a]	11	12	13	15	
Cases of BBD[b]	128	137	108	97	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.11 (0.88–1.42)	0.86 (0.66–1.11)	0.76 (0.58–1.00)	0.02
Multivariate[c]	1.00 (referent)	1.13 (0.89–1.44)	0.88 (0.68–1.14)	0.79 (0.61–1.04)	0.05
Vitamin A (including supplements)					
Intake (IU/day)[a]	6316	9399	12771	19634	
Cases of BBD[b]	121	142	108	99	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.18 (0.92–1.50)	0.91 (0.70–1.18)	0.81 (0.62–1.06)	0.04
Multivariate[c]	1.00 (referent)	1.17 (0.91–1.49)	0.92 (0.71–1.20)	0.84 (0.64–1.11)	0.07
Retinol					
Intake (IU/day)[a]	1486	2023	2697	5145	
Cases of BBD[b]	112	129	128	101	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.19 (0.92–1.53)	1.17 (0.91–1.51)	0.94 (0.72–1.23)	0.72
Multivariate[c]	1.00 (referent)	1.21 (0.93–1.56)	1.21 (0.94–1.57)	0.99 (0.72–1.38)	0.71
Total carotenoids					
Intake (IU/day)[a]	4012	6622	9466	16228	
Cases of BBD[b]	120	129	117	104	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.08 (0.84–1.38)	0.98 (0.76–1.26)	0.85 (0.65–1.10)	0.17
Multivariate[c]	1.00 (referent)	1.07 (0.83–1.37)	0.96 (0.74–1.25)	0.87 (0.67–1.14)	0.19
α-Carotene					
Intake (mcg/day)[a]	353	694	1074	2105	
Cases of BBD[b]	114	123	127	106	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.08 (0.84–1.40)	1.11 (0.86–1.43)	0.91 (0.70–1.19)	0.58
Multivariate[c]	1.00 (referent)	1.07 (0.83–1.39)	1.09 (0.85–1.41)	0.93 (0.71–1.22)	0.44
β-Carotene					
Intake (mcg/day)[a]	1753	2814	3952	6252	
Cases of BBD[b]	123	127	113	107	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.04 (0.81–1.33)	0.92 (0.72–1.19)	0.87 (0.67–1.12)	0.18
Multivariate[c]	1.00 (referent)	1.04 (0.81–1.33)	0.92 (0.71–1.19)	0.88 (0.68–1.15)	0.24
β-Cryptoxanthin					
Intake (mcg/day)[a]	63	122	189	287	
Cases of BBD[b]	111	130	114	115	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.15 (0.89–1.48)	1.01 (0.78–1.31)	1.02 (0.79–1.33)	0.87
Multivariate[c]	1.00 (referent)	1.17 (0.90–1.51)	1.02 (0.78–1.33)	1.04 (0.80–1.36)	0.92
Lycopene					
Intake (mcg/day)[a]	3604	5190	7152	12119	
Cases of BBD[b]	110	124	136	100	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.15 (0.89–1.48)	1.26 (0.98–1.62)	0.95 (0.73–1.25)	0.98
Multivariate[c]	1.00 (referent)	1.16 (0.90–1.51)	1.31 (1.01–1.69)	0.97 (0.74–1.27)	0.56
Lutein & zeaxanthin					
Intake (mcg/day)[a]	1022	1674	2387	3841	
Cases of BBD[b]	125	108	130	107	
RR (95% CI)					
Age-adjusted	1.00 (referent)	0.88 (0.68–1.13)	1.05 (0.82–1.34)	0.88 (0.68–1.14)	0.58
Multivariate[c]	1.00 (referent)	0.86 (0.66–1.11)	1.04 (0.82–1.33)	0.88 (0.68–1.14)	0.57
Folate					
Intake (mcg/day)[a]	233	286	333	421	
Cases of BBD[b]	122	127	114	107	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.05 (0.82–1.35)	0.95 (0.74–1.22)	0.95 (0.73–1.23)	0.43
Multivariate[c]	1.00 (referent)	1.07 (0.83–1.38)	0.97 (0.75–1.26)	1.00 (0.76–1.31)	0.84

[a] Values for intake are medians of each quartile, adjusted for total energy intake using the residual method.
[b] A total of 470 cases of histologically confirmed proliferative BBD occurred during the follow-up period.
[c] The multivariate models are adjusted for the following: age in months, time period (3 periods), total energy intake (quartiles), age at menarche (<12, 12, 13, or ≥14 years), menopausal status (premenopausal, postmenopausal, or uncertain), body mass index at age 18 (<19, 19–20.4, 20.5–21.9, 22–24.9, or ≥25 kg/m^2), history of breast cancer in mother or sister (yes/no), alcohol intake between ages 18 and 22 (0, <5, 5–14, or ≥15 g/day), and multivitamin use between ages 13 and 18 (yes/no).

Table 4 RRs and 95% CIs of proliferative BBD among 29,494 women followed from 1991 to 1997, according to intakes of fiber, fruits, and vegetables during adolescence

	Cases of BBD[a]	Age-adjusted RR	Multivariate RR[b]
Fiber (g/day, energy-adjusted)			
Quartile 1 (lowest)	133	1.00 (referent)	1.00 (referent)
Quartile 2	118	0.91 (0.71–1.17)	0.94 (0.73–1.21)
Quartile 3	127	0.96 (0.75–1.22)	0.99 (0.78–1.27)
Quartile 4 (highest)	92	0.71 (0.54–0.92)	0.75 (0.57–0.98)
P for trend		0.03	0.05
Fruits (servings/day)			
<1	92	1.00 (referent)	1.00 (referent)
1.0–1.9	150	0.97 (0.74–1.25)	0.95 (0.73–1.23)
2.0–2.9	128	0.97 (0.74–1.27)	0.96 (0.73–1.27)
≥3	100	0.84 (0.64–1.12)	0.85 (0.63–1.16)
P for trend		0.25	0.34
Vegetables (servings/day)			
<2	157	1.00 (referent)	1.00 (referent)
2.0–2.9	138	1.02 (0.81–1.28)	1.02 (0.81–1.29)
3.0–3.9	99	1.15 (0.89–1.48)	1.17 (0.90–1.52)
≥4	76	0.93 (0.71–1.23)	0.97 (0.72–1.30)
P for trend		0.96	0.91
Fruits and vegetables combined (servings/day)			
<3	93	1.00 (referent)	1.00 (referent)
3.0–3.9	88	1.11 (0.83–1.48)	1.10 (0.82–1.48)
4.0–4.9	96	1.23 (0.92–1.63)	1.23 (0.92–1.65)
5.0–5.9	70	1.11 (0.82–1.52)	1.12 (0.81–1.55)
≥6	123	0.97 (0.74–1.27)	1.00 (0.74–1.35)
P for trend		0.66	0.77

[a] A total of 470 cases of histologically confirmed proliferative BBD occurred during the follow-up period.
[b] The multivariate models are adjusted for the following: age in months, time period (3 periods), total energy intake (quartiles), age at menarche (<12, 12, 13, or ≥14 years), menopausal status (premenopausal, postmenopausal, or uncertain), body mass index at age 18 (<19, 19–20.4, 20.5–21.9, 22–24.9, or ≥25 kg/m^2), history of breast cancer in mother or sister (yes/no), alcohol intake between ages 18 and 22 (0, <5, 5–14, or ≥15 g/day), and multivitamin use between ages 13 and 18 (yes/no).

similar but older population (27) examined the impact of recall bias by comparing observed associations between fat intake and breast cancer risk using prospective and retrospective diet assessments; the investigators found some differences in the direction and magnitude of observed associations based on the timing of the diet assessment. In this study, however, both diet assessments referred to a time period only a few years before the breast cancer diagnosis. A disease diagnosis may have a greater effect on recall of recent diet than on recall of diet in the remote past. Other studies have shown little or no difference between cancer cases and controls in the reliability of long-term recall (28–30). Furthermore, whereas the relationship between fat and breast cancer has been the focus of numerous epidemiological studies and has received substantial attention in the popular press, increasing the chance that participants would be aware of hypothesized associations, there has been little information about the association of diet with BBD in the scientific literature or popular press, making it less likely that recall bias could explain the findings of the present study.

A related issue is the influence of adult diet on recall of adolescent diet. If current diet is strongly correlated with recall of past diet and is related to risk of BBD, then current diet could confound observed associations between adolescent intake and BBD. However, as mentioned earlier, the average correlation between two separate recalls of foods consumed during high school in a similar population was much higher than the correlation between current consumption of those foods and the first recall of high school diet (22). Furthermore, women participating in the present study were younger than the women in the previous reproducibility study when they completed the high school diet questionnaire, which should lead to more accurate recall.

Recall bias and the influence of current diet on recall of adolescent diet may be particularly relevant to the findings for vitamin E. Although their clinical efficacy has not been proven, vitamin E supplements have been used to treat symptoms of BBD for a number of years (31, 32). Therefore, a greater proportion of women with a confirmed diagnosis or symptoms of BBD may be taking vitamin E supplements compared with women with no diagnosis or symptoms. If women with BBD who are currently taking vitamin supplements have a tendency to over-report their use of vitamin supplements in high school, this could bias the estimate of the association between adolescent vitamin E intake and proliferative BBD, making vitamin E look less protective. However, because the reported prevalence of multivitamin use during high school (15.7%) among women in the study was fairly low, and the correlation between adolescent vitamin E intake and adult vitamin E intake reported in 1991 ($r = 0.12$) was small, it is unlikely that this bias had an important impact on our results. Alternatively, if study participants were aware of a potential inverse association between vitamin E intake and BBD, it is possible that women with BBD may have under-reported their use of vitamin supplements during adolescence compared with noncases, which could induce a spurious inverse association between vitamin E and BBD. This type of biased recall is also unlikely, however, given that the hypothesized association between vitamin E intake and BBD has not been widely publicized and that supplements accounted for only slightly more than 1% of total vitamin E intake during adolescence among participants.

Another limitation of the study pertains to the comparability between actual and recalled adolescent diet. The validity of recall of adolescent diet 20–40 years later has not been established, and nondifferential misclassification of partici-

pants' true consumption of foods and nutrients could bias associations toward the null. A study is currently being conducted to examine the reproducibility and validity of recall of adolescent diet in this cohort. The reproducibility study conducted in a similar cohort showed moderately high correlations between two separate recalls, 8 years apart, of consumption of 24 food items during adolescence (22). Studies that have examined the validity of recall of diet from the distant past in other populations have had mixed results (20, 28). Given the exploratory nature of this analysis and the absence of dietary data actually recorded during adolescence, however, recall of adolescent diet currently provides the best available information on diet during this time period. Future studies that collect data on childhood and adolescent diet prospectively are needed to confirm these findings.

Uncontrolled confounding is always a possibility in observational research. Although it is unlikely that adolescent diet is strongly correlated with adult risk factors for BBD, it may be associated with other early life and adolescent lifestyle exposures that affect risk of BBD and breast cancer (although few such exposures have been identified to date). To address this concern, we have presented age-adjusted results as well as results adjusted for age and time period, age at menarche, body mass index at age 18, alcohol intake between 18 and 22 years, multivitamin use during adolescence, family history of breast cancer, and menopausal status. The age-adjusted and multivariate RRs were very similar, suggesting that there is minimal confounding by these known risk factors for breast cancer. Although there may be some degree of confounding by other factors, it is unlikely that uncontrolled confounding could entirely account for our findings.

Many dietary factors were considered in this study, which may increase the probability of observing a falsely significant result simply due to chance. Because the comparisons of interest were specified before the data were examined, it was not necessary to make a uniform adjustment to the significance level (33). Readers should exercise caution, however, in the interpretation of the results, paying close attention to internal consistency, findings from other studies, and biological plausibility.

The similar findings for vegetable fat and vitamin E provide evidence for internal consistency; both vegetable fat and vitamin E intakes during adolescence were inversely associated with incidence of BBD, and vegetable oils are a major source of vitamin E. Other evidence for internal consistency comes from the analyses of food sources of nutrients. Although foods were not the primary focus of this study, the findings for the individual foods and food groups that were examined were generally consistent with the results from the nutrient analyses. For example, nuts contain vegetable fat, and nut consumption was inversely associated with incidence of proliferative BBD. Higher consumption of all meat and red meat were associated with increased risk of proliferative BBD, which is consistent with the positive associations for animal fat and monounsaturated fat. In addition to demonstrating internal consistency, the findings are compatible with those from a recent retrospective study in a similar cohort, in which higher consumption of vegetable fat and fiber during adolescence were related to lower breast cancer risk (21), and with those from a retrospective case-control study in British Columbia, in which consumption of vegetable oils in childhood was associated with reduced risk of premenopausal breast cancer (18).

Biological plausibility of the observed associations should also be considered in the interpretation of these findings. Fiber has been hypothesized to be related to lower breast cancer risk by decreasing circulating levels of estrogens, which stimulate proliferation of mammary cells. Fiber inhibits reabsorption of estrogens in the gastrointestinal tract (34) and has been associated with increased levels of sex-hormone binding globulin, which binds to estrogen and thereby reduces its bioavailability (35). Vitamin E has long been believed to be protective against the development of some cancers, including breast cancer, through its function as an antioxidant, neutralizing free radicals that can cause DNA damage and thereby inhibiting mutagenesis and cell transformation (7, 8). More recently, vitamin E has also been shown to induce apoptosis *in vitro* and to inhibit the growth of breast cancer cells *in vitro* and *in vivo* (36). The effects of these and other nutrients may be particularly important during adolescence because cells of the mammary gland are undergoing rapid development between menarche and first birth and, thus, may be vulnerable to malignant transformation (16, 17). Data from epidemiological studies on the relationship between intakes of vitamin E and fiber and breast cancer have yielded weak and inconsistent results (9, 37–41). Our results suggest that previous studies may have had null findings because they were focusing on diet during adulthood, which may not be the most relevant time period.

An important strength of this study is our definition of proliferative BBD. There is likely to be some misclassification in the reporting of BBD because BBD is a heterogeneous group of lesions and may be confused with other breast disorders. This misclassification could result in attenuation of the effect estimates. Restricting the outcome definition to cases for whom tissue samples were available and using a uniform, centralized pathology review to classify the cases as proliferative or nonproliferative reduces the likelihood of misclassification. A small study that was conducted to examine inter-rater reliability showed that the pathologists' classification of the confirmed cases as proliferative or nonproliferative was highly reproducible.[6] The decision to focus only on proliferative cases was based on evidence from a number of studies showing that proliferative lesions are associated with increased risk of breast cancer, whereas nonproliferative lesions do not confer any increase in risk (1). These findings suggest that proliferative BBD is the most etiologically relevant indicator of breast cancer risk.

In summary, this study examined the relationship between intakes of fats and micronutrients during adolescence and incidence of proliferative BBD. These results suggest that monounsaturated fat intake is positively associated with risk of proliferative BBD, whereas vegetable fat, vitamin E, and fiber intakes are inversely associated with risk. Confirmation of these associations may suggest a means for prevention of breast cancer.

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RISK FACTORS FOR BREAST CARCINOMA *IN SITU* VS. INVASIVE BREAST CANCER IN A PROSPECTIVE STUDY OF PRE- AND POSTMENOPAUSAL WOMEN, 1996–2002. *K Reinier, P Vacek, B Geller (University of Vermont, Burlington, VT, 05405)

To examine factors associated with breast carcinoma *in situ* versus invasive breast cancer, we used prospective data from the Vermont Breast Cancer Surveillance System (VBCSS), a statewide mammography and breast pathology registry. Subjects were 61,844 women (61% postmenopausal) with no prior breast cancer and at least one mammogram between April 1, 1996 and June 30, 2001, and who were followed until they had at least one additional mammogram before July 1, 2001, a benign biopsy before June 30, 2002, or development of breast cancer. A total of 1,191 breast cancers (300 *in situ* and 891 invasive) were diagnosed. The mean follow-up was 3.1 years (s.d. 1.1). Cox regression models were used to estimate the relative risks (RR) of *in situ* and invasive cancer associated with family history of breast cancer, age at first childbirth or nulliparity, postmenopausal hormone use, body mass index (BMI), and breast density. Risk factors for *in situ* and invasive cancer in premenopausal women were similar, with the exceptions of childbearing and BMI. Later age at first childbirth and nulliparity were more strongly associated with *in situ* than invasive cancer. Higher BMI was slightly but non-significantly protective for invasive cancer and was not associated with *in situ* cancer. In postmenopausal women, risk factors for *in situ* and invasive cancer were also similar, except that higher BMI was associated with increased risk of invasive cancer (RR = 1.9 for highest vs. lowest BMI category, 95% confidence interval (CI) 1.4, 2.5), but was not associated with *in situ* cancer (RR = 0.9, 95% CI 0.5, 1.4).

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BODY FATNESS AT YOUNG AGES AND INCIDENCE OF PREMENOPAUSAL BREAST CANCER. *H J Baer, G A Colditz, and W C Willett for the Nurses' Health Study II Research Group (Harvard University, Boston, MA, 02115)

Obesity during adulthood has been associated with breast cancer incidence, but the role of body fatness earlier in life is less clear. We examined body fatness at young ages in relation to incidence of premenopausal breast cancer. Participants were 109,244 premenopausal women in the Nurses' Health Study II who recalled their somatotype (body build) at ages 5, 10, and 20 using a validated 9-level pictogram and were free from cancer in 1989. During 12 years of follow-up, 1,308 cases of breast cancer were confirmed by review of pathology reports. Cox proportional hazards regression was used to compute incidence rate ratios (RR) and 95% confidence intervals (CI) for body fatness at each age while adjusting for potential confounders. Body fatness at ages 5, 10, and 20 were each inversely associated with breast cancer incidence, with the greatest reduction for age 5; the multivariate RR was 0.55 (95% CI: 0.42, 0.74) for somatotype level 5 or greater at age 5 compared to level 1 (P for trend <0.001). The multivariate RR was 0.47 (95% CI: 0.34, 0.65) for childhood somatotype (average of ages 5 and 10) 5 or greater compared to 1 (P for trend <0.001). With additional adjustment for the average of body mass index (BMI) at age 18 and recent BMI, the multivariate RR for childhood somatotype 5 or greater was 0.54 (95% CI: 0.39, 0.75), and the trend remained statistically significant ($p = 0.01$). Adjustment for menstrual cycle characteristics had little impact on the multivariate rate ratios for childhood somatotype. These results indicate that greater body fatness at young ages is independently associated with lower incidence of premenopausal breast cancer.

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ORAL CONTRACEPTIVE ANDROGENICITY AND OVARIAN CANCER RISK. *J Greer, F Modugno, G Allen, R Ness. (University of Pittsburgh, Pittsburgh PA 15261)

Oral contraceptives (OCs) have been consistently linked to reduced risk of ovarian cancer. Compared to older products, recent OC formulations contain lower progestin content with varying degrees of androgenicity. Recent data linking androgens to ovarian cancer, especially in women with endometriosis, suggests that the androgenicity of an OC may impact it efficacy in preventing ovarian cancer. Methods: We investigated whether the protection associated with OCs might differ according to their androgenicity using data from the SHARE Study, a population-based case-control study of ovarian cancer (567 incident cases, 1,019 healthy controls with complete OC formulation data). OC data were collected by a standardized in-person interview and were categorized by the androgenicity of their progestin component. Multivariate logistic regression was used to assess the association of OC androgencity with ovarian cancer, while controlling for the potential confounders of age, parity, family history of ovarian cancer, and tubal ligation. Results: Androgenic and non-androgenic OCs conferred a similar and significant reduction in ovarian cancer risk (OR = 0.51; 95% CI = 0.31, 0.83 and OR = 0.56; 95% CI = 0.43, 0.73, respectively). Among women with endometriosis (26 cases, 36 controls), androgenic formulations conferred less protection than non-androgenic formulations (OR = 0.61 vs. 0.25). No differences in duration of use, age at first use, and time since last use were found between androgenic and non-androgenic formulations. Conclusion: In general, the androgenicity of an OC does not alter its chemopreventive efficacy, although women with endometriosis may receive less protection from androgenic formulations

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ANTHROPOMETRIC MEASURES, ALCOHOL CONSUMPTION, AND THE RISK OF OVARIAN CANCER. *K Berger, F Modugno, and R Ness (University of Pittsburgh, Pittsburgh, PA 15261)

Background: Height, weight and body mass index have inconsistently been associated with ovarian cancer. We investigated the association between anthropometric measures and ovarian cancer in a large, population based case-control study of ovarian cancer conducted from 1993–1998. Methods: Cases (767) aged 20–69 with a recent diagnosis of epithelial ovarian cancer were compared with community controls (1367). Unconditional logistic regression models were used to assess the association between ovarian cancer and quartiles of anthropometric measurements as determined by the control population distribution. Adjustments were made for age, family history of ovarian cancer, race, oral contraceptive (OC) use, parity, and history of tubal ligation. Because lifestyle factors such as alcohol consumption, smoking and OC use may affect weight or hormone levels, we further examined the effect of these factors on any observed associations. Results: Increasing weight at age 18 (OR 1.04, 1.34, 1.35 for comparison of quartiles 2, 3, and 4 with quartile 1) and at age 30 (OR 1.23, 1.61, 1.26) was associated with a modest and significant increase in ovarian cancer risk. Greater current weight was associated with ovarian cancer in general (OR 1.12, 1.27 1.24 for quartiles 2, 3 and 4) and among ever drinkers (OR 1.54, 2.19 1.68), but not among never drinkers (OR 0.93, 0.86, 0.99). Alcohol consumption alone was not associated with ovarian cancer. No other significant associations or interactions were observed. Conclusions: Increasing weight over the lifecourse is a risk factor for ovarian cancer. The association between current weight and ovarian cancer is strongly affected by alcohol consumption.

A Prospective Study of Diet and Benign Breast Disease

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Abstract

Much attention has been paid to the relation between diet and breast cancer risk. Because benign breast disease (BBD), particularly atypical hyperplasia (AH), is a marker of increased breast cancer risk, studies of diet and BBD may provide evidence about the effect of diet at an early stage in the process of breast carcinogenesis. We evaluated the relationship between fat, fiber, antioxidant and caffeine intake and incidence of non-proliferative BBD, proliferative BBD without atypia and AH in the Nurses' Health Study II. We calculated rate ratios (RR) and 95% confidence intervals (95% CI) for each quartile of energy-adjusted intake using the lowest quartile as reference. There was no increase in risk of BBD with increasing fat intake, rather increasing vegetable fat was associated with a significant reduction in the rate of proliferative BBD without atypia. There was no significant association between any type of BBD and micronutrient intake. High caffeine consumption was positively associated (RR = 2.46, 95% CI 1.11-5.49 for the highest quartile), and use of multivitamin supplements inversely associated (RR = 0.57, 95% CI 0.33-0.98) with risk of AH although these analyses were based on small numbers. These data do not support the hypothesis that higher fat consumption increases risk of BBD, with or without atypia, and also provide little evidence for a major role of antioxidants in the development of breast disease. They do, however, raise the possibility that high caffeine intake may increase, and use of vitamin supplements may decrease risk of developing AH. (Cancer Epidemiol Biomarkers Prev 2004;13(7):1106–13)

Introduction

Breast cancer is the most common cancer among women in America and throughout the developed world, but it occurs much less frequently in Asia (1). Women who move from countries with low breast cancer risk to countries with high risk acquire the higher breast cancer risk of their destination (2), suggesting that potentially modifiable, and, therefore, preventable, environmental factors, such as diet, influence breast cancer risk. Results from studies evaluating the relationship between adult diet and breast cancer are, however, inconsistent. Higher breast cancer incidence rates are consistently seen in countries with higher per capita consumption of fat (3). In contrast, case-control studies have generally reported only modest increases in risk of breast cancer associated with increased dietary fat intake (4), whereas prospective studies have found little evidence for an association (5). Attention has also focused on the potential role of antioxidants in breast cancer development, but again the data are largely inconsistent (5, 6).

One reason for the inconsistent results might be that dietary exposures may be more important at earlier stages in the disease process than are commonly considered in epidemiologic studies of cancer (7). Benign proliferative epithelial disorders of the breast, particularly those showing signs of atypia, are associated with approximately 1.5- and 4-fold increased risks of cancer, respectively, compared with women with non-proliferative breast tissue (8-10), suggesting that they may be a marker for subsequent breast cancer. Studies of the relation between diet and benign breast disease (BBD), thus, offer an opportunity to evaluate the role of diet at an earlier stage in the process of breast carcinogenesis.

Several studies that attempted to evaluate the relationship between dietary factors and BBD have reported conflicting results. Some studies found that fat intake was associated with increased risk of proliferative BBD (7), and particularly of atypical hyperplasia (AH) (11), but other studies found no association (12, 13). Increased intake of vitamin A supplements (14) and retinol and carotene (7) has been associated with reduced risk of BBD, although the latter effects were seen only in comparison to community controls (unbiopsied) and not compared with a second control group of women who underwent biopsy but were not found to have proliferative BBD. Other studies have reported no association between these nutrients and BBD (12, 13, 15). Reduced risks have also been reported for increased intake of vitamins C (12) and E (15), and vitamin E has been used for treatment of BBD, but again these effects

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have not been confirmed by others (16). Early reports suggested that methylxanthines (caffeine, theobromine, and theophylline) might influence risk of BBD (17, 18) and that caffeine restriction improved symptoms of BBD (19). However, this has not been supported by more recent studies (20) although in one study total methylxanthine intake was positively associated with risk of BBD with severe atypia in comparison to community controls (21).

Many of these studies were hampered by relatively small numbers of women with confirmed BBD. Furthermore, the majority of the previous studies were retrospective introducing the possibilities of both selection and recall bias. We evaluated the relationship between some dietary factors and subsequent diagnosis of BBD in a cohort of 58,628 U.S. women. Specific hypotheses were that higher total fat and saturated fat intake would be associated with increased risks of proliferative BBD but that higher intake of vegetable or monounsaturated fat, vitamin A, carotenoids and vitamins C and E would be associated with reduced risk. We also evaluated the relationship between caffeine intake and risk of developing proliferative disease with or without atypia.

Methods

The Nurses' Health Study II is a prospective cohort study that began in 1989 when 116,671 female nurses ages 25 to 44 years completed a mailed questionnaire about their medical history and lifestyle. Subsequent questionnaires requesting updated information on risk factors and medical events, including diagnosis of BBD, have been mailed to the women every 2 years. In 1991, the questionnaire included a 133-item food frequency questionnaire. The protocol for the study was approved by the Human Research Committees of the Brigham and Women's Hospital and the Harvard School of Public Health, Boston, MA.

Study Population. Follow-up for the present study began in 1991 when diet was first measured. We excluded 18,864 women (16%) who did not complete the food frequency questionnaire and 2,361 (2%) who had incomplete dietary data (more than 70 food items blank) or implausible total energy intake (<800 or >4,200 kcal/d). We also excluded women who reported BBD (n = 32,217) or cancer other than non-melanoma skin cancer (n = 754) before 1991 as well as 3,079 women who were pregnant when they completed the dietary questionnaire because of concerns that the reported dietary data might not have reflected their usual intake. This left a baseline cohort of 59,396 women. A total of 768 women (1.3%) did not contribute any follow-up information and a further 817 (1.4%) and 1,696 (2.9%) were excluded in 1993 and 1995, respectively, because they had no further follow-up information after that point.

Dietary Measures. The food frequency questionnaire measures intake of a wide variety of nutrients and dietary factors and has shown good validity in similar study populations (correlations for energy-adjusted nutrients with dietary records are generally 0.60 to 0.70). The validity of a similar questionnaire was assessed among 191 older women in the Nurses' Health Study by comparison with two 1-week diet records (average r for all nutrients = 0.62; ref. 22). In this latter validation, correlations for energy-adjusted nutrients (without supplements) de-attenuated for week-to-week variation in the diet records were 0.57 for total fat, 0.68 for saturated fat, 0.48 for polyunsaturated fat, 0.58 for monounsaturated fat, 0.79 for total vitamin A, and 0.76 for vitamin C. Nutrients calculated from the food frequency questionnaire are correlated with their corresponding biochemical indicators: plasma β-carotene (r = 0.30-0.42; refs. 23-25), plasma vitamin E (r = 0.41-0.53; refs. 23-25), plasma folate (r = 0.35-0.51; refs. 26, 27), adipose linoleic acid (r = 0.35-0.37; refs. 24, 28), adipose *trans* fatty acid (r = 0.51; ref. 28), and adipose N-3 fatty acids (r = 0.48-0.49; refs. 24, 28).

Reported BBD. In 1993, 1995, and 1997, the women were asked if, since the previous questionnaire, a physician had told them they had fibrocystic or other BBD and, if so, if this had been confirmed by tissue biopsy or aspiration. Two definitions of reported BBD were considered: firstly, all new reports of BBD and secondly a subgroup comprising only those cases reported as confirmed by biopsy. The date of diagnosis of BBD was estimated as the mid-point between the date of return of the questionnaire reporting incident BBD and the return date of the most recent questionnaire before that. Women who reported BBD and breast cancer on the same questionnaire were excluded from the case groups and from further follow-up because it was not possible to determine the relative timing of the two diagnoses.

Histologically Confirmed BBD. Women who reported a diagnosis of biopsy-confirmed BBD on the 1993, 1995, or 1997 questionnaires were contacted to seek confirmation of the diagnosis and permission to obtain their pathology records. Of the 1,956 women who reported biopsy-confirmed BBD and who also had valid dietary data, 1,577 (81%) confirmed the diagnosis and granted permission for review of the pathology slides and records from their biopsy. The main reasons for non-response were that the woman could not be contacted (7%), did not confirm she had had a biopsy (7%), or did not give permission for her slides to be reviewed (6%). Adequate pathology material was obtained and reviewed for 1,409 women (89% of those who confirmed the biopsy and gave permission). Of these, 1,328 (94%) were confirmed to be eligible cases and a valid diagnosis was obtained. The main reasons for exclusion were that the pathology specimen did not contain breast tissue (n = 37) or the biopsy date was before the start of follow-up (n = 22). In addition, women were excluded if their biopsy date was after the date they reported BBD (n = 8) or if they had a diagnosis of breast cancer within 1 year of diagnosis of BBD (n = 3), or a diagnosis of carcinoma *in situ* (n = 5). Women without valid pathology material did not differ significantly from eligible women for whom material was available with respect to age, family history of breast cancer, body mass index (BMI), use of oral contraceptives (OC), or total fat or vitamin intake.

The benign breast lesions were initially classified by one of four pathologists (S.J.S., J.L.C., T.J., or G.P.) as normal or non-proliferative, proliferative without atypia, or AH. This classification was done after standard training and according to standard criteria (29). In a reiability study, a random sample of 53 cases (22 normal/

non-proliferative, 31 proliferative) was re-reviewed in a blinded fashion by a second pathologist and the results were found to be highly reproducible (κ = 0.72). In addition, a proportion of biopsies were jointly reviewed by two pathologists to ensure consistency and any biopsy specimens that showed atypia or questionable atypia were jointly re-reviewed (by S.J.S., J.L.C., and T.J. or G.P.) and a consensus diagnosis reached. Specimens with intraductal papilloma, radial scar, sclerosing adenosis, fibroadenoma, fibroadenomatous change, or moderate to florid ductal hyperplasia in the absence of AH were classified as proliferative without atypia.

Statistical Analysis. Each participant contributed person-time of follow-up from the time she returned the dietary questionnaire in 1991 until the first of any of the following: return date of the 1997 questionnaire, death from any cause, diagnosis of BBD, report of cancer other than non-melanoma skin cancer, or loss to follow-up. For dietary variables, energy-adjusted estimates of nutrient intake (30) were categorized by quartiles based on the distribution of intakes in the cohort. Dietary factors considered were: fat (total, animal, vegetable, saturated, monounsaturated, and polyunsaturated fats), fiber, vitamin A, retinol (equivalents of vitamin A), vitamin C, vitamin E (α-tocopherol), carotene, folate, and caffeine. Women were also classified as users or non-users of vitamin supplements (multivitamins and/or vitamins A, C, E, β-carotene, and folic acid).

For time-varying covariates, such as OC use and BMI, cases and person-time were updated every 2 years. Cox proportional hazards regression was used to estimate rate ratios (RR) and 95% confidence intervals (95% CI) compared with women in the lowest quartile of intake, after controlling for potential confounders. Estimates were adjusted for age (months), time period (three 2-year periods), history of breast cancer in mother or sister (yes/no), BMI (<21, 21-22.9, 23-24.9, 25-29.9, 30+), OC use (never, past, current), total energy intake (quartiles), and use of vitamin supplements (yes/no). Further adjustment for age at menarche, smoking status, menopausal status, and parity did not appreciably alter the effect estimates and these variables were not included in the final models. Tests for trend across quartiles of intake were conducted by assigning the median intake in each quartile to all women in that category and treating these values as a continuous variable.

In addition, case-case comparisons were conducted among the subgroup of women with histologically confirmed BBD to reduce the possibility of bias due to selective referral of women for biopsy. Logistic regression was used to calculate prevalence odds ratios and 95% CI after adjusting for confounders.

Results

Between 1991 and 1997, the 58,628 women in the analysis contributed 321,973 person-years of follow-up. The distributions of selected characteristics of the population at baseline are shown in Table 1 according to intake of total fat, vitamin E and caffeine, and use of vitamin supplements. Women in the highest quartile of fat intake were more likely to be current smokers and less likely to be nulliparous than women in the lowest quartile of fat intake. They also had lower intake of vitamin E (and other vitamins, data not shown), were less likely to take vitamin supplements, and had higher caffeine intake. The opposite trends were seen for women with high and low vitamin E intake. High caffeine intake was positively associated with current smoking.

Reported BBD. During follow-up, a total of 9,645 women reported a physician diagnosis of BBD and, of those, 1,956 women (20.3%) reported that this diagnosis was confirmed by tissue biopsy. After adjustment, total fat intake (RR = 1.06, 95% CI 1.00-1.12 for the highest versus lowest quartile, P for trend = 0.03), vegetable fat (RR = 1.07, 95% CI 1.01-1.13, P = 0.007), monounsaturated fat (RR = 1.07, 95% CI 1.01-1.13, P = 0.03), and polyunsaturated fat (RR = 1.11, 95% CI 1.05-1.18, P = 0.002) were all positively associated with any report of physician-diagnosed BBD, but the associations were weak. Intakes of total vitamin A (RR = 0.92, 95% CI 0.87-0.98,

Table 1. Age-standardized percentages* and means for characteristics of 58,628 participants at baseline according to total fat, vitamin E, caffeine, and vitamin supplement intake

	Total fat†		Total vitamin E†		Caffeine†		Supplements	
	Q1	Q4	Q1	Q4	Q1	Q4	No	Yes
Number of women	14,393	14,844	15,680	13,162	13,823	14,788	30,580	28,048
Percentage of group								
History of breast cancer in mother or sister	5	5	5	5	5	5	5	5
Age at menarche <12 years	25	25	23	25	23	26	25	24
Premenopausal in 1991	98	98	98	97	98	98	98	98
Nulliparous in 1991	33	24	24	32	24	29	24	28
Current smoker in 1991	10	16	15	11	4	24	13	11
Current OC user in 1991	12	12	13	12	12	11	13	12
User of dietary supplements in 1991	55	41	12	96	52	44	0	100
Mean for group								
Age in 1991 (y)	36	36	35	36	35	37	36	36
BMI in 1991 (kg/m^2)	24	26	25	24	25	25	25	24
Total fat intake (g/day, energy adjusted)	49	77	63	62	62	65	64	62
Vitamin E intake (mg/day, energy adjusted)	27	19	7	64	24	21	8	36
Caffeine intake (mg/day, energy adjusted)	224	278	263	233	27	557	260	235

*Standardized to the age distribution of the cohort in 1991 (except age in 1991).
†Q1 = lowest and Q4 = highest quartile of energy-adjusted nutrient residuals.

P = 0.002) and retinol (RR = 0.91, 95% CI 0.85-0.97, P = 0.001) were inversely associated with any report of BBD. However, these effects were no longer seen when the analyses were restricted to a more stringent case group, including only those cases of BBD that were reported as confirmed by tissue biopsy. In contrast, increasing intake of vegetable fat was associated with a statistically significantly lower rate of biopsy-confirmed BBD (RR = 0.84 for the highest versus lowest quartile, 95% CI 0.74-0.95, P for trend = 0.009). Use of vitamin supplements (multivitamins, vitamins A, C, E, β-carotene, and/or folate) was also associated with a lower rate of reported biopsy-confirmed BBD, regardless of the type of supplements used (RR = 0.89, 95% CI 0.81-0.97 for any supplement use versus no supplements). There was no association between intake of animal fat, saturated fat,

Table 2. RRs and 95% CIs for the association between fat and fiber intake and incidence of histologically confirmed BBD among 58,628 women ages 27 to 46 and followed from 1991 to 1997

Quartiles of daily intake* range (median)		Non-proliferative BBD (n = 475)			Proliferative BBD without atypia (n = 786)			Atypical hyperplasia (n = 67)		
		Cases	RR†	(95% CI)	Cases	RR†	(95% CI)	Cases	RR‡	(95% CI)
Total energy (kcal)										
≤1,390	(1,178)	129	1.0		206	1.0		19	1.0	
1,391-1,732	(1,565)	116	0.91	(0.70-1.16)	203	1.01	(0.83-1.22)	19	1.11	(0.59-2.10)
1,733-2,127	(1,912)	109	0.86	(0.66-1.10)	191	0.95	(0.78-1.16)	14	0.80	(0.40-1.61)
≥2,128	(2,448)	121	0.95	(0.74-1.22)	186	0.93	(0.76-1.14)	15	0.98	(0.50-1.94)
			P = 0.7§			P = 0.4§			P = 0.8§	
Total fat (g)										
≤55.7	(50.5)	118	1.0		196	1.0		14	1.0	
55.8-63.1	(59.7)	108	0.90	(0.70-1.18)	198	1.01	(0.83-1.23)	11	0.78	(0.35-1.71)
63.2-70.6	(66.7)	123	1.02	(0.79-1.31)	189	0.96	(0.79-1.18)	26	1.73	(0.90-3.33)
≥70.7	(75.9)	126	1.03	(0.80-1.34)	203	1.01	(0.83-1.23)	16	0.97	(0.47-2.01)
			P = 0.6			P = 1.0			P = 0.6	
Animal fat (g)										
≤28.9	(25.0)	116	1.0		178	1.0		18	1.0	
29.0-34.5	(31.9)	116	1.00	(0.77-1.29)	200	1.12	(0.91-1.37)	19	1.02	(0.54-1.96)
34.6-40.5	(37.3)	116	1.01	(0.78-1.31)	194	1.10	(0.90-1.35)	19	1.03	(0.54-1.97)
≥40.6	(45.3)	127	1.08	(0.83-1.39)	214	1.16	(0.95-1.42)	11	0.54	(0.26-1.15)
			P = 0.5			P = 0.2			P = 0.1	
Vegetable fat (g)										
≤22.6	(19.5)	121	1.0		227	1.0		11	1.0	
22.7-27.5	(25.2)	119	0.97	(0.75-1.25)	189	0.82	(0.67-0.99)	13	1.14	(0.51-2.55)
27.6-33.0	(30.1)	114	0.91	(0.71-1.18)	189	0.82	(0.67-0.99)	22	1.82	(0.88-3.76)
≥33.1	(37.3)	121	0.98	(0.76-1.26)	181	0.79	(0.65-0.96)	21	1.76	(0.85-3.67)
			P = 0.8			P = 0.02			P = 0.07	
Saturated fat (g)										
≤19.2	(17.1)	112	1.0		187	1.0		12	1.0	
19.3-22.3	(20.9)	124	1.05	(0.81-1.36)	198	1.03	(0.84-1.26)	14	1.10	(0.51-2.39)
22.4-25.4	(23.8)	114	1.01	(0.78-1.31)	208	1.14	(0.93-1.39)	29	2.40	(1.22-4.72)
≥25.5	(27.8)	125	1.08	(0.83-1.40)	193	1.02	(0.83-1.25)	12	0.93	(0.42-2.08)
			P = 0.6			P = 0.7			P = 0.6	
Monounsaturated fat (g)										
≤20.7	(18.5)	120	1.0		191	1.0		14	1.0	
20.8-23.9	(22.4)	120	1.02	(0.79-1.32)	195	1.06	(0.87-1.30)	13	0.96	(0.45-2.03)
24.0-27.2	(25.5)	104	0.84	(0.65-1.10)	185	0.98	(0.80-1.20)	21	1.42	(0.72-2.81)
≥27.3	(29.5)	131	1.08	(0.84-1.39)	215	1.13	(0.93-1.38)	19	1.19	(0.59-2.38)
			P = 0.8			P = 0.3			P = 0.5	
Polyunsaturated fat (g)										
≤9.4	(8.5)	107	1.0		216	1.0		15	1.0	
9.5-11.0	(10.3)	124	1.17	(0.90-1.51)	204	0.94	(0.78-1.14)	18	1.21	(0.61-2.41)
11.1-12.8	(11.9)	127	1.22	(0.94-1.58)	172	0.80	(0.65-0.98)	16	1.00	(0.49-2.03)
≥12.9	(14.3)	117	1.15	(0.89-1.50)	194	0.93	(0.77-1.13)	18	1.14	(0.57-2.28)
			P = 0.3			P = 0.3			P = 0.8	
Fiber (g)										
≤14.7	(12.9)	113	1.0		204	1.0		14	1.0	
14.8-17.6	(16.2)	131	1.20	(0.93-1.55)	198	1.00	(0.82-1.22)	16	1.23	(0.60-2.54)
17.7-21.0	(19.2)	109	1.03	(0.79-1.34)	190	0.98	(0.80-1.20)	18	1.40	(0.69-2.82)
≥21.1	(24.0)	122	1.16	(0.89-1.50)	194	0.99	(0.81-1.21)	19	1.44	(0.72-2.89)
			P = 0.5			P = 0.9			P = 0.3	

*Adjusted for total energy using the residual method (except total energy).
†RR adjusted for age (months), time period, total energy intake (quartiles), supplement use (any/none), history of breast cancer in mother or sister, OC use (current, past, never), BMI (<21, 21-22.9, 23-24.9, 25-29.9, 30+).
‡RR adjusted for age (months), time period, total energy intake (quartiles), supplement use (any/none), history of breast cancer in mother or sister.
§Test for linear trend across quartiles (defined according to the median intake).

Table 3. RRs and 95% CIs for the association between total intake of selected micronutrients (including supplements) and incidence of histologically confirmed BBD among 58,628 women ages 27 to 46 and followed from 1991 to 1997

Quartiles of daily intake* range (median)		Non-proliferative BBD (n = 475)			Proliferative BBD without atypia (n = 786)			Atypical hyperplasia (n = 67)		
		RR†	(95% CI)	Cases	RR†	(95% CI)	Cases	RR‡	(95% CI)	(95% CI)
Vitamin A (IU)										
≤7,643	(5,701)	133	1.0		180	1.0		19	1.0	
7,644-11,100	(9,323)	115	0.92	(0.72-1.19)	208	1.21	(0.99-1.49)	15	0.92	(0.46-1.81)
11,101-15,752	(13,088)	116	0.97	(0.75-1.25)	212	1.31	(1.07-1.61)	12	0.80	(0.38-1.68)
≥15,753	(20,075)	111	0.93	(0.71-1.22)	186	1.14	(0.92-1.42)	21	1.57	(0.80-3.06)
			P = 0.7§			P = 0.4§			P = 0.2§	
Vitamin C (mg)										
≤106	(81)	141	1.0		209	1.0		19	1.0	
107-158	(131)	123	0.90	(0.70-1.15)	211	1.05	(0.87-1.28)	12	0.73	(0.35-1.51)
159-250	(193)	107	0.82	(0.62-1.08)	189	1.03	(0.83-1.27)	23	1.88	(0.99-3.60)
≥251	(425)	104	0.79	(0.58-1.08)	177	0.98	(0.76-1.26)	13	1.47	(0.61-3.55)
			P = 0.2			P = 0.7			P = 0.3	
Vitamin E (mg α-tocopherol)										
<7.7	(6.8)	141	1.0		225	1.0		18	1.0	
7.7-9.6	(8.5)	116	0.84	(0.66-1.08)	213	0.95	(0.78-1.14)	22	1.36	(0.72-2.58)
9.7-16.2	(11.9)	105	0.85	(0.63-1.14)	185	0.89	(0.71-1.11)	15	1.40	(0.65-3.03)
>16.2	(22.9)	113	1.02	(0.73-1.41)	163	0.84	(0.65-1.09)	12	1.41	(0.54-3.68)
			P = 0.4			P = 0.2			P = 0.6	
Retinol (equivalents of vitamin A, μg)										
≤1,130	(867)	135	1.0		197	1.0		21	1.0	
1,131-1,685	(1,384)	112	0.86	(0.67-1.11)	208	1.07	(0.88-1.31)	14	0.72	(0.37-1.42)
1,686-2,524	(2,044)	123	1.02	(0.79-1.33)	202	1.16	(0.94-1.43)	17	1.17	(0.60-2.29)
≥2,525	(3,258)	105	0.93	(0.69-1.24)	179	1.07	(0.85-1.34)	15	1.26	(0.59-2.66)
			P = 0.8			P = 0.6			P = 0.4	
Carotene (IU)										
≤4,911	(3,455)	125	1.0		174	1.0		17	1.0	
4,912-7,541	(6,199)	124	1.02	(0.79-1.31)	211	1.23	(1.00-1.50)	16	0.92	(0.46-1.82)
7,542-11,364	(9,137)	100	0.82	(0.63-1.08)	205	1.17	(0.96-1.44)	12	0.69	(0.33-1.45)
≥11,365	(15,187)	126	1.04	(0.81-1.34)	196	1.12	(0.91-1.38)	22	1.32	(0.69-2.52)
			P = 0.9			P = 0.6			P = 0.3	
Folate (μg)										
≤278	(234)	127	1.0		202	1.0		20	1.0	
279-371	(320)	124	1.00	(0.78-1.29)	210	1.06	(0.87-1.29)	22	1.15	(0.63-2.12)
372-611	(461)	118	1.03	(0.78-1.36)	208	1.13	(0.91-1.40)	13	0.88	(0.42-1.85)
≥612	(781)	106	1.07	(0.77-1.48)	166	1.06	(0.82-1.37)	12	1.21	(0.48-3.04)
			P = 0.7			P = 0.7			P = 0.8	
Use of vitamin supplements										
No		255	1.0		426	1.0		45	1.0	
Yes		220	0.96	(0.80-1.15)	360	0.94	(0.82-1.08)	22	0.56	(0.33-0.93)
Caffeine (mg)										
≤62	(24)	108	1.0		185	1.0		8	1.0	
63-171	(124)	125	1.07	(0.83-1.39)	192	0.97	(0.79-1.19)	18	2.08	(0.90-4.79)
172-381	(266)	116	0.97	(0.74-1.26)	187	0.90	(0.73-1.11)	15	1.49	(0.63-3.52)
≥382	(491)	126	1.06	(0.82-1.38)	222	1.04	(0.85-1.27)	26	2.46	(1.11-5.49)
			P = 0.8			P = 0.7			P = 0.06	

*Adjusted for total energy using the residual method.
†RR adjusted for age (months), time period, total energy intake (quartiles), supplement use (any/none), history of breast cancer in mother or sister, OC use (current, past, never), BMI (<21, 21-22.9, 23-24.9, 25-29.9, 30+).
‡RR adjusted for age (months), time period, total energy intake (quartiles), supplement use (any/none), history of breast cancer in mother or sister.
§Test for linear trend across quartiles (defined according to the median intake).

fiber, caffeine, vitamins C and E, carotene, or folate and report of any BBD or biopsy-confirmed BBD.

Histologically Confirmed BBD. Tables 2 and 3 show the relationship between the dietary variables and incidence of histologically confirmed BBD. The results are shown separately for non-proliferative BBD (475 cases), proliferative BBD without atypia (786 cases), and AH (67 cases).

As for reported biopsy-confirmed BBD, increasing intake of vegetable fat was associated with significantly lower rates of proliferative BBD without atypia; however, it was also associated with somewhat higher rates of AH (Table 2). None of the other types of fat were associated with any diagnosis of BBD. There was also no association between fiber intake and rates of non-proliferative BBD or proliferative BBD with or without atypia.

Table 3 shows the association between total intake of selected micronutrients (from dietary sources and supplements combined) and histologically confirmed BBD. Increasing intake of vitamin C was associated with a lower rate of non-proliferative BBD while increasing vitamin E intake was associated with lower rates of proliferative BBD without atypia; however, neither of these effects reached statistical significance (Table 3). Intakes of vitamin A, retinol, carotene, and folate were not associated with either non-proliferative or proliferative BBD. There was also no association with either α-carotene or β-carotene when these were considered separately (data not shown). Similar patterns were seen when only dietary sources of micronutrients were considered, but intake of dietary vitamin E was now also associated with a reduced rate of non-proliferative BBD (RR = 0.78, 95% CI 0.61-1.01 for the highest versus lowest quartiles, *P* for trend = 0.08).

Somewhat different patterns were seen when the case-group was restricted to the 67 women diagnosed with AH although interpretation of these results is difficult because of the small number of cases. There were no clear associations with total intake (or dietary intake only, results not shown) of individual vitamins (Table 3); however, use of vitamin supplements (multivitamins and/or vitamins A, C, E, β-carotene, or folate) was associated with an almost 50% lower rate of atypia (RR = 0.56, 95% CI 0.33-0.93). A similar effect was seen for multivitamin supplements alone (RR = 0.57, 95% CI 0.33-0.98). A significantly higher rate of AH was seen among women in the highest quartile of caffeine intake with a RR of 2.46 (95% CI 1.11-5.49, *P* for trend = 0.06) for women in the fourth quartile compared with the lowest quartile. Neither supplement use nor caffeine intake was related to either non-proliferative BBD or proliferative BBD without atypia.

To ensure that the associations seen for caffeine and supplement use and rates of atypia were not biased by selective referral of women for biopsy, we conducted additional case-case analyses comparing women with a histological diagnosis of proliferative BBD without atypia and women with AH to those with non-proliferative disease. As expected, there was no association with proliferative BBD without atypia but both caffeine (prevalence odds ratios = 2.43, 95% CI 1.04-5.72 for the highest versus lowest quartiles) and supplement use (prevalence odds ratios = 0.59, 95% CI 0.34-1.02) were associated with AH.

To explore these relations more thoroughly, additional analyses were conducted for food groups that contribute to fat and micronutrient intake. Foods considered included dairy foods, red meat, fruit and vegetables and also breakfast cereals because these are commonly fortified with multivitamins. We observed a weak positive association between increasing consumption of dairy foods (*P* for trend = 0.05), particularly high fat dairy foods (whole milk, cream, ice cream, high-fat cheeses, and butter, *P* for trend = 0.04) and rates of non-proliferative BBD. Proliferative BBD without atypia was unrelated to any of the food groups considered but the rate of AH was lower among women who ate one or more servings of breakfast cereal per day compared with those who ate it less than once a week (RR = 0.26, 95% CI 0.06-1.09).

Discussion

These data provide no support for the hypothesis that high total fat or saturated fat intake is associated with development of proliferative BBD. This adds weight to the belief that these fats also do not play a major role in the development of breast cancer, although it is possible that they could influence breast cancer risk among women with BBD. Modest increases in the rates of non-proliferative BBD were seen with increasing consumption of high fat dairy foods but this type of BBD does not seem to be associated with an increased risk of breast cancer (8). Women in the highest total fat intake groups were no more likely to be diagnosed with proliferative BBD with or without atypia than women with lower fat intake. We did, however, observe lower rates of proliferative BBD with increasing consumption of vegetable fat and this association persisted after adjustment for vitamin E intake (vegetable fat is a major source of vitamin E). This inverse association is consistent with data suggesting that increasing intake of vegetable fat in adolescence may also be associated with a lower risk of proliferative BBD (RR = 0.73, 95% CI 0.55-0.96 for the highest versus lowest quartile (31).

The lack of association between increased total fat intake and BBD is consistent with several earlier reports (16, 32), including another prospective study conducted within a breast cancer screening study (13), although three studies had previously suggested a positive association (7, 11, 14). Fat intake was positively associated with BBD in a retrospective comparison of 383 women with biopsy-confirmed proliferative BBD and 192 women who underwent biopsy but were not found to have proliferative BBD (7) but this association disappeared after adjustment for total energy intake. Furthermore, in the same study, there was no association with fat when the women with BBD were compared with 383 unbiopsied community controls. In a second retrospective study conducted in Israel, 107 women with atypical lesions reported higher consumption of all foods than both hospital and community controls (11). This difference was attributed primarily to increased consumption of foods containing more than 10% fat although the authors were not able to adjust for energy intake. The third study reported an increased risk of atypia associated with highest consumption of meat and dairy fat; however, this was based on only 32 cases with atypia and the assessment of diet was based on reported intake of only 39 food items selected for their fat or vitamin A content (14).

Increasing fiber intake was not associated with risk of BBD overall or with the non-proliferative and proliferative subtypes considered separately. In contrast, high fiber intake in adolescence was associated with a significantly lower risk of proliferative BBD (31).

Our findings, along with those from case-control studies (7, 12) and another prospective study (13), provide little support for an association between vitamin intake and BBD overall. Women with higher intakes of vitamin E had a modest reduction in risk of proliferative BBD and women with higher intake of vitamin C were slightly less likely to be diagnosed with non-proliferative BBD, but neither of these associations reached statistical significance. The weak association between vitamin E

and proliferative BBD is, however, consistent with a non-significant effect reported for vitamin E intake in adolescence and incidence of BBD (RR = 0.79, 95% CI 0.61-1.04; ref. 31). Experimental data have suggested that vitamin E can inhibit mammary tumors in rodents (33), and vitamin E has long been used for treatment of BBD (34), although randomized trials have not shown any benefits of vitamin E over placebo (35, 36). Two retrospective studies have evaluated the association between vitamin E and risk of BBD, one reporting no association (16) while the other, in contrast to the present results, found increasing intake was associated with a reduction in risk of AH but not proliferative BBD without atypia (10). Both this latter study and the present analysis included relatively few women with atypia, making it difficult to draw clear conclusions about this group. There is little evidence to support an association between vitamin E and breast cancer risk (37-39).

Use of vitamin supplements (multivitamins, vitamins A, C, E, β-carotene, or folate) was associated with a significantly reduced risk of reported biopsy-confirmed BBD. When the different histological subtypes of BBD were considered separately, the association was restricted to AH with no association seen for non-proliferative BBD or proliferative BBD without atypia. This apparent protective effect may be due either to the combination of multiple vitamins in the supplements or to some other component of multivitamins, or alternatively, use of vitamin supplements may be a marker for some other lifestyle factor that is associated with a reduced risk of BBD. The RRs were adjusted for age and family history of breast cancer, and allowing for other factors, including OC use, BMI and age at menarche, parity and menopausal status, did not appreciably alter the estimates. Furthermore, the association between most of these factors and BBD is weak, suggesting that the relation with supplement use is not due to uncontrolled confounding. The observation that a reduced risk of AH was also seen among women eating the highest levels of breakfast cereal, a food item that is commonly supplemented with multiple vitamins, strengthens belief that it might be the combination of vitamins that is important.

Initial reports from uncontrolled and unrandomized studies suggested that caffeine restriction improved BBD symptomatology. It was suggested that methylxanthines (caffeine, theobromine, and theophylline) inhibited cyclic adenosine monophosphate and guanylic acid and activated a protein kinase leading to overproduction of fibrous tissue and cystic fluid and, thus, BBD. Caffeine, from coffee, tea, and chocolate, is the major dietary methylxanthine. Results of studies investigating the association between caffeine and/or methylxanthine intake and BBD are, however, conflicting. Two early hospital-based case-control studies found no association between a discharge diagnosis of BBD and coffee consumption (40, 41) while a third found a significant positive association between coffee consumption and both a history and clinically diagnosed BBD among pairs of twins (42). More recent studies have required histologic confirmation of BBD and have evaluated the risk separately for different types of BBD. Of these, two studies reported significant positive associations that were strongest among women with high-risk types of BBD (17, 18) while a third found no association overall but an increased risk among the 40 women with severe atypia (21). Two other studies, however, did not find any association with BBD either overall or among the subgroup with atypia (20, 43).

To our knowledge, ours is the first prospective study to evaluate the relation between caffeine consumption and diagnosis of BBD and our data do not support the hypothesis that caffeine intake influences risk of BBD overall. However, consistent with three of five previous retrospective studies, we observed a significantly increased risk of AH associated with increasing caffeine intake.

A major problem in any study of BBD is that of identifying cases. It is possible that more health-conscious women with lower fat and higher vitamin intake might be more likely to identify and seek advice for a breast lump and, thus, be diagnosed with BBD, thereby biasing measures of effect upward. However, given the increasing awareness among women about breast cancer, it seems unlikely that members of this cohort of registered nurses would differ appreciably in their propensity to seek advice. Furthermore, the results were essentially the same when the analysis was restricted to women who had undergone some form of breast screening (mammography or examination by a physician) in the previous 2 years, and who, therefore, had similar opportunity for diagnosis of BBD. In addition, the positive association with caffeine intake and the inverse association with supplement use persisted when women with atypia were compared with women who were also biopsied for BBD but diagnosed with non-proliferative disease. It is, therefore, highly unlikely that these effects could be due to selective referral of high coffee drinkers and/or supplement users for biopsy.

Advantages of the present study include the high follow-up rates and the centralized review of pathology slides to ensure consistency. Another major strength is that diet was measured before women were diagnosed with BBD thereby ruling out the possibility for recall bias. However, risk factors may exert their effect many years before diagnosis of disease, thus, it is possible that the dietary exposures in the present study (measured a maximum of 6 years before diagnosis) may be too recent to be associated with incidence of BBD. Although it is likely that recent diet will reflect past diet, any misclassification is likely to bias estimates of effect toward the null. It is also possible that exposures much earlier in life may be important and this suggestion is supported by the observation that stronger apparent protective effects for vegetable fat and vitamin E were seen in an evaluation of adolescent diet and risk of proliferative BBD in adulthood (31) than in the present analyses.

In conclusion, the present data suggest that higher total fat and saturated fat consumption is not associated with an increased risk of BBD. This adds weight to the argument that high-fat diets also do not play a major role in the development of breast cancer although it is possible that they could influence breast cancer risk among women with BBD. The data also provide little evidence for a major role of micronutrients, including vitamins A, C, and E in development of breast disease, but do raise the possibility that high caffeine intake may increase, and use of vitamin supplements decrease risk of developing atypia. The suggestion that risk factors might vary for proliferative BBD with and without atypia is interesting;

however, despite the large size of this cohort, only a relatively small number of women were confirmed histologically as having atypia making it difficult to draw clear conclusions about this group. This emphasizes the requirement for future studies to be large enough to have sufficient power to be able to evaluate risk factors separately for proliferative disease and AH.

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EXPLORATION OF RESIDENTIAL HISTORY AND BREAST CANCER RISK IN WISCONSIN USING GEOGRAPHIC INFORMATION SYSTEMS. *J A McElroy, P L Remington, S A Robert, J M Hampton, A Trentham-Dietz (University of Wisconsin, Madison, WI 53726)

Little research has focused on domestic migration and breast cancer risk although is it well known that migration can effect the detection of geographic differences in disease risk. Using geographic information systems (GIS), the relation between geographic mobility and breast cancer risk was examined using a population-based case-control study in Wisconsin. Breast cancer cases 20–69 years of age and diagnosed in 2000–2002 (n = 1,441) were identified from the statewide Wisconsin cancer registry. Female controls of similar age were randomly selected from population lists (n = 1,421). Lifetime residential history (residing for 1 or more years), including name of town, village, city, and county was collected through interviews approximately 1 year after diagnosis. Number of moves was dissimilar for cases (16% moved 1 time; 18% moved 6+ times) and controls (14% moved 1 time; 19% moved 6+ times). After adjustment for the common risk factors, compared to women who had never moved, the relative risk of breast cancer for women who had moved six or more times in their lifetime was 0.73 (confidence interval (CI) 0.52, 1.02; p-trend 0.01). The relative risk was 1.11 (CI 0.94, 1.30) for women who had lived exclusively in rural areas in Wisconsin in the 1990s compared to women who had lived in urban areas. Spatially, the geographic mobility of participants varied by region. Maps highlighting nuances in geographic mobility will be presented. These analyses provide evidence of the importance of ascertaining residential history to more accurately characterize the contribution of place in relation to breast cancer risk.

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PERCEIVED RISK AND FAMILY HISTORY OF BREAST CANCER IN THE GENERAL POPULATION. *I J Hall, R Uhler, J Audrain-McGovern (Centers for Disease Control and Prevention, Atlanta, GA, 30341)

Research has shown that women often overestimate their breast cancer risk causing undue anxiety and worry. Excess anxiety and worry may deter some women from breast cancer screening. We sought to determine to what extent women overestimate their actual risk as defined by their family history. Women without a personal history of breast cancer were selected from the 2000 National Health Interview Study (NHIS). Weighted frequencies were determined for perception of risk and for level of risk conferred by family history using SUDAAN. Family history risk was categorized as high (>2 relatives with breast cancer or 1 relative diagnosed <50 years), moderate (1 relative diagnosed >50 years), or average (0 relatives with breast cancer). High and moderate risk family history was reported by 3.4% and 4.0% of women, respectively. After weighting, almost 50% of women may have overestimated their risk. Of 14,685 women with no family history of breast cancer, 1,481 (10.1 % (95% confidence interval (CI) 9.5, 10.6)) perceived themselves to be at high risk of cancer and 4,237 (39.3% (95% CI 29.5, 31.1)) perceived themselves to be at moderate risk of cancer. A comparison of perceived risk with family history risk can assess the accuracy of one aspect of risk perception. The differences reported in risk perception vs. family history risk suggest that women may benefit from educational efforts designed to help them gain a truer perspective of their risk for breast cancer based on family history. A more realistic perception may appease anxiety and worry and promote adherence to screening recommendations.

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OBESITY AND BREAST CANCER SURVIVAL AMONG YOUNG WOMEN. *Abrahamson P E, Gammon M D, Lund M J, Eley W, Flagg E W, Porter P, Brinton L A, Coates R J. (University of North Carolina, Chapel Hill, NC)

For post-menopausal women, obesity is a well-established risk factor for breast incidence and survival. However, among pre-menopausal women obesity may reduce the risk of developing breast cancer, but little is known regarding its effect on prognosis. This study investigated whether obesity at diagnosis influences breast cancer survival among a cohort of young women. A population-based follow-up study was conducted among 1264 women aged 20–54 years who were diagnosed with invasive breast cancer between 1990–1992 in Atlanta and New Jersey. Cases were interviewed within several months of diagnosis, and asked about their weight and height at age 20 and the year prior to diagnosis. Study personnel performed a variety of anthropometric measures at the interview. With 8–10 years of follow-up time, all-cause mortality status was determined through the National Death Index (n = 290 deaths). An increased risk of death was observed for the group with high body mass index (BMI) at the time of interview (>30) compared to normal weight (BMI = 18.5, 24.9) women [stage, income, and waist-to-hip ratio (WHR) adjusted hazard ratio (HR) = 1.57, 95% confidence interval (CI)= 1.16, 2.12]. A similar result was seen for the highest vs. lowest quartile of WHR [stage, income, and BMI adjusted HR = 1.57, 95% CI = 1.10, 2.24]. The strongest association was found for women who were overweight or obese (BMI ≥25) at age 20 as well as at the time of diagnosis [stage, income and WHR adjusted HR = 2.15, 95% CI = 1.44, 3.22] compared to those with a normal weight at both time periods. This study provides evidence that breast cancer survival is reduced among pre-menopausal women who are obese.

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TUBAL STERILIZATION IN RELATION TO BREAST CANCER RISK. *A H Eliassen, G A Colditz, B Rosner, S E Hankinson, for the Nurses' Health Study Research Group (Harvard University, Boston, MA 02115)

Tubal sterilization methods cause varying degrees of damage to tissue surrounding the fallopian tubes, including the utero-ovarian artery. Disruption of ovarian blood supply may lead to hormonal dysfunction and thus, a decreased risk of breast cancer. We conducted a prospective analysis within the Nurses' Health Study to assess the relation of tubal sterilization to breast cancer risk. A total of 77,560 women, aged 30 to 55 and free of cancer, were followed from 1976 to June 2000. Data on tubal sterilization as a form of contraception were collected biennially from 1976 to 1982. In 1994, data were collected on history of and age at tubal sterilization. At baseline, 11,217 women reported tubal sterilization. We documented 4,130 cases of invasive breast cancer through follow-up. Cox proportional hazards models, adjusting for age, parity, age at first birth, age at menopause, hormone use, and other breast cancer risk factors, provided estimated rate ratios (RRs) and 95% confidence intervals (CIs). Overall, women with tubal sterilization had a similar risk of breast cancer as other women, RR = 0.95, 95% CI (0.88, 1.03). Results varied by calendar year, but not by age at or time since procedure. Tubal sterilizations performed from 1970 to 1975 decreased risk, RR = 0.85, 95% CI (0.75, 0.97), while procedures performed before 1970 or after 1975 were not associated with risk, RR = 0.99, 95% CI (0.85, 1.17), RR = 1.02, 95% CI (0.91, 1.14), respectively. Although there is no overall association between tubal sterilization and breast cancer risk, these data suggest a modest inverse association at a time when unipolar electrocautery, which caused extensive damage, was commonly used.

Association between plasma prolactin concentrations and subsequent risk of breast cancer

Shelley S. Tworoger, A. Heather Eliassen, and Susan E. Hankinson for the Nurses Health Study Research Group

Prolactin is important in human breast development and substantial laboratory and *in vitro* data suggest a role in mammary carcinogenesis. Although several epidemiological studies, including the Nurses' Health Study, have suggested that elevated circulating prolactin concentrations are associated with an increased breast cancer risk among postmenopausal women, there was relatively low power to examine associations by breast cancer subtype or characteristics of the study population. Therefore, we conducted a prospective, nested case-control study within the Nurses' Health Study cohort to examine, in further detail, the association between plasma prolactin concentrations and postmenopausal breast cancer; also using our unique resources we were able to assess the independent contribution of prolactin after adjusting for estradiol concentrations. Blood samples were collected from cohort members in 1989 and 1990; prolactin concentrations were measured by microparticle enzyme immunoassay. The analysis included 852 cases of postmenopausal breast cancer diagnosed after blood donation and before June 2000, who had one or two controls (n=1,275) that were matched on age, postmenopausal hormone use, fasting status, and time of day and month of blood collection. Statistical analyses used multivariate conditional logistic regression for the main effect and unconditional logistic regression adjusted for matching factors for the stratified analyses. Relative risks (RR) and 95% confidence intervals (CI) compare women in the highest versus lowest quartiles of prolactin concentrations. Plasma prolactin was associated with an increased risk of postmenopausal breast cancer (RR: 1.35, 95% CI: 1.04-1.75, p-trend = 0.01). The association differed by estrogen receptor (ER)/progesterone receptor (PR) status (p=0.005). The RR was 1.77 (95% CI: 1.28-2.47, p-trend = 0.001) for ER+/PR+ breast cancers, 0.74 (95% CI: 0.43-1.29, p-trend=0.25) for ER-/PR-, and 1.71 (95% CI: 0.90-3.25, p-trend = 0.19) for ER+/PR- breast cancers. Too few cancers were ER-/PR+ (n=20) to consider separately. Associations generally were similar for ductal (RR: 1.42, 95% CI: 1.06-1.90, p-trend = 0.004) and lobular carcinomas (RR: 1.76, 95% CI: 0.95-3.26, p-trend = 0.11). The association among ER+/PR+ cancers did not significantly differ by postmenopausal hormone (PMH) use, age at blood draw, or years between blood draw and diagnosis. Among women not using PMH at blood draw, the RR for ER+/PR+ cancers was 1.86 (95% CI: 1.13-3.07, p-trend=0.02) after adjustment for estradiol. In conclusion, our prospective data suggest that plasma prolactin concentrations are associated with an increased risk of postmenopausal breast cancer, particularly for estrogen and progesterone receptor positive cancers, independently of estradiol. We are currently examining the association between prolactin and breast cancer among premenopausal women.

Endogenous steroid hormone concentrations and the risk of breast cancer among postmenopausal women

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While relations between endogenous hormones and breast cancer risk among postmenopausal women have been reported, little research has focused on tumor invasiveness or receptor status or on the association with endogenous progesterone. We prospectively evaluated these relations with a case-control study nested within the Nurses' Health Study. Blood samples were collected in 1989-90, and from among the 11,169 women who were postmenopausal and not using postmenopausal hormones (PMH) at baseline, 322 cases of breast cancer were reported through June 1998. Two controls were selected per case and matched on age, fasting status, and month and time of day of blood collection (n=637). In conditional logistic regression analyses, controlling for established breast cancer risk factors, we consistently observed a significant direct relation with both estrogens and androgens, but did not find any important relation between progesterone or SHBG levels and breast cancer risk. The effect of estrogen levels was strongest among those who had never used PMH, and, despite small numbers, all hormones tended to be associated most strongly with *in situ* disease. The most striking relations were observed among those tumors that were both estrogen and progesterone receptor positive. Comparing the highest to the lowest quartiles, we observed a 3-fold increased risk for estradiol (multivariate relative risk (RR) = 3.3, 95% confidence interval (CI) = 2.0-5.4) and 2-fold for testosterone (RR = 1.9, CI = 1.2-3.4), androstenedione (RR = 2.5, CI = 1.4-4.3), and DHEAS (RR = 2.3, CI = 1.3-4.1) among ER+/PR+ cases. These observations support the relation between endogenous steroid hormones and breast cancer risk and suggest that circulating hormones may most strongly influence risk of ER+/PR+ tumors.

Table. Relative risk (95% CI) of breast cancer by quartile category of plasma hormone levels.

Estradiol, pg/mL¥					
MV RR †	1.0 (ref)	1.3 (0.9-1.9)	1.1 (0.7-1.7)	2.1 (1.5-3.2)	p-value‡ <0.001
In situ cases	1.0 (ref)	1.9 (0.7-4.8)	1.1 (0.4-3.7)	3.0 (1.2-7.4)	0.01
Never PMH use	1.0 (ref)	1.6 (0.9-3.0)	1.9 (1.0-3.7)	3.6 (2.0-6.4)	<0.001
ER+/PR+	1.0 (ref)	1.8 (1.0-3.0)	1.5 (0.8-2.8)	3.3 (2.0-5.4)	<0.001
ER-/PR-	1.0 (ref)	1.0 (0.4-2.2)	0.5 (0.2-1.7)	1.0 (0.4-2.4)	0.46
Estrone sulfate, pg/mL	<178	178-279	280-421	>421	
MV RR †	1.0 (ref)	1.6 (1.0-2.5)	1.4 (0.9-2.2)	2.4 (1.6-3.8)	<0.001
In situ cases	1.0 (ref)	2.0 (0.6-6.4)	2.4 (0.8-7.3)	3.5 (1.2-10.2)	0.03
Never PMH use	1.0 (ref)	1.5 (0.8-3.0)	1.7 (0.9-3.3)	3.2 (1.8-5.9)	<0.001
ER+/PR+	1.0 (ref)	1.5 (0.8-2.7)	1.6 (0.9-3.0)	2.8 (1.6-4.9)	<0.001
ER-/PR-	1.0 (ref)	1.5 (0.6-4.0)	0.9 (0.3-2.7)	1.9 (0.7-4.8)	0.34
Progesterone, ng/dL	<1.6	1.7-4.0	4.1-8.0	>8.0	
MV RR †	1.0 (ref)	1.1 (0.7-1.7)	1.1 (0.7-1.7)	0.9 (0.6-1.5)	0.90
In situ cases	1.0 (ref)	2.9 (1.1-7.6)	1.2 (0.4-3.5)	1.6 (0.5-5.0)	0.67
ER+/PR+	1.0 (ref)	1.3 (0.7-2.3)	1.3 (0.8-2.2)	1.3 (0.7-2.4)	0.38
ER-/PR-	1.0 (ref)	0.9 (0.3-2.4)	1.1 (0.5-2.6)	0.3 (0.1-1.3)	0.17
Testosterone, ng/dL	<15	15-19	20-26	>26	
MV RR †	1.0 (ref)	0.9 (0.6-1.4)	1.5 (1.0-2.2)	1.6 (1.0- 2.4)	<0.001
In situ cases	1.0 (ref)	1.7 (0.5-5.5)	3.1 (1.0-9.3)	3.7 (1.2-11.0)	0.01
ER+/PR+	1.0 (ref)	0.9 (0.5-1.7)	1.8 (1.1-3.1)	2.0 (1.2-3.4)	<0.001
ER-/PR-	1.0 (ref)	0.4 (0.2-1.1)	0.6 (0.3-1.6)	0.7 (0.3-1.6)	0.35

CI = confidence interval; MV = multivariate

Sample size: all women = 320 cases, 634 controls; *in situ* cases = 41; never PMH cases = 204; ER+/PR+ cases = 152; ER-/PR- cases = 38.

‡ P-value, test for trend. The logarithm of the hormone level was entered into the model as a continuous variable; two-sided.

¥ Batch-specific quartile cutpoints were used to categorize estradiol.

† Conditional logistic regression models controlling for body mass index at age 18, family history of breast cancer, age at menarche, age at first birth and parity, age at menopause, and duration of PMH use were used in the main analyses among all women. Unconditional logistic regression, controlling additionally for the matching factors were used for subgroup analyses.

Abstract for "Breast Cancer Research at Harvard" Symposium
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Adult Recall of Adolescent Diet: Reproducibility and Comparison with Maternal Reporting

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Abstract

Many cancers have long latency periods and dietary factors during adolescence that may plausibly impact cancer occurrence in adulthood. Although prospective studies assessing food intake among children and adolescents have begun, most will require many more decades of follow-up to reach clinical endpoints. A more timely way, although potentially less ideal, to assess the relation between adolescent diet and cancer is to collect diet data retrospectively from adults. In of the few studies examining very distant diet, the authors evaluated a 125-item food frequency questionnaire (HS-FFQ) assessing diet during high school (15-35 years in the past) completed by 45,947 women in the Nurses' Health Study II (NHSII) cohort. To assess reproducibility, the HS-FFQ was re-administered, approximately four years later, to 333 of these women. In addition, 272 mothers of the NHSII participants reported their daughter's adolescent diet using the HS-FFQ. For reproducibility, the mean Pearson correlation (r) for 38 nutrient intakes was 0.65 (range 0.50-0.77), and the mean Spearman rank correlation for food intakes was 0.60 (range 0.37-0.77). Current adult diet was only weakly correlated with recall of adolescent diet (mean r=0.20 for nutrient intakes). For the comparison of the HS-FFQs between the NHSII women and their mothers, the mean Pearson correlation was 0.40 (range 0.13-0.59) for nutrients and the mean Spearman rank correlation was 0.30 (range 0.10-0.61) for foods. While further studies are warranted, our findings imply that this food frequency questionnaire provides a reasonable record of diet during adolescence for use in assessing associations between early diet and adult disease.

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Adult Recall of Adolescent Diet: Reproducibility and Comparison with Maternal Reporting

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Abbreviations: BMI, body mass index; BMR, basal metabolic rate; HS-FFQ, High School Food Frequency Questionnaire; IRB, Institutional Review Board; NHS, Nurses Health Study; NHSII, Nurses Health Study II; r, correlation; WHO, World Health Organization.

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Abstract

Many cancers have long latency periods and dietary factors during adolescence may plausibly impact cancer occurrence in adulthood. Due to lack of prospective data, retrospective collection of adolescent diet is essential. The authors evaluated a 124-item food frequency questionnaire (HS-FFQ) assessing diet during high school (15-35 years in the past) that was completed by 45,947 women in the Nurses' Health Study II (NHSII) cohort. To assess reproducibility, the HS-FFQ was re-administered, approximately four years later, to 333 of these women. The mean Pearson correlation for 38 nutrient intakes was 0.65 (range 0.50-0.77), and the mean Spearman rank correlation for food intakes was 0.60 (range 0.37-0.77). Current adult diet was only weakly correlated with recall of adolescent diet (mean r=0.20 for nutrient intakes). To assess validity, 272 mothers of the NHSII participants reported their daughter's adolescent diet using the HS-FFQ. In this comparison, the mean Pearson correlation was 0.40 (range 0.13-0.59) for nutrients and the mean Spearman rank correlation for foods was 0.30 (range 0.10-0.61). While further studies are warranted, our findings imply that this food frequency questionnaire provides a reasonable record of diet during adolescence.

adolescent; diet; mothers; nutrition; questionnaires; reproducibility of results

Many common cancers have long latencies that may span several decades between the onset of the carcinogenic process and clinical detection (1). Dietary factors during adolescence may plausibly impact cancer occurrence in adulthood by enhancing or deterring carcinogenic processes (2). Adolescence is characterized by hormonal changes and rapid proliferation of incompletely differentiated tissues in several organs. Thus, adolescence may be a more etiologically relevant period than adulthood to study potential causal and preventive determinants of some cancers (3-5). A better understanding of which dietary factors are important in the etiology of cancer and the period of life in which they act is critical.

Although prospective studies assessing food intake among children and adolescents have begun, most will require many more decades of follow-up to reach clinical endpoints (1). A more timely way, although potentially less ideal, to assess the relation between adolescent diet and cancer is to collect the data retrospectively from adults. If these dietary data are collected before disease occurrence, recall bias is avoided.

A crucial component to the conduct and interpretation of studies using retrospective dietary assessments is the evaluation of the questionnaire instrument. Recall of adolescent diet as an adult will be prone to measurement error because it primarily relies on memory of diet in the distant past. Several studies have reported reasonable validity and reproducibility of recalled diet up to 10 years in the past (6-9). However, greater uncertainty exists for recall exceeding 10 years (10, 11).

We evaluated a food frequency questionnaire (HS-FFQ) that asked women in the Nurses' Health Study II cohort (NHSII) about foods they ate during high school, between the ages of 13

and 18. This paper reports on: 1) the reproducibility of this questionnaire, using recalled adolescent diet information provided by participants collected at two different time points; 2) a maternal comparison in which these recalled data are compared with high school diet information provided by mothers of NHSII participants; and 3) the influence of current adult diet on the recall of adolescent diet by NHSII participants.

MATERIALS AND METHODS

Study Participants

The NHSII is an on-going, prospective cohort study consisting of 116,671 female registered nurses. When the study was initiated in 1989, participants were between the ages of 25 and 42. Every two years, participants have been sent a follow-up questionnaire asking about the use of hormones, lifestyle practices, and diagnoses of chronic disease. Every four years, participants also receive a semiquantitative food frequency questionnaire to report their current diet. The study has maintained a response rate of 90 percent or greater (12).

The HS-FFQ, a supplementary questionnaire administered in 1998, was completed by 45,947 NHSII women. To assess reproducibility, 400 women were randomly selected from these initial participants to complete a second HS-FFQ in 2002. To minimize recall bias of past diet due to existing disease, those who had cancer, heart disease, or asthma were excluded from the second sample. This second HS-FFQ was completed by 347 out of 400 women (86 percent). Fourteen women were subsequently excluded based on established dietary criteria (caloric intake <600 or >5000 kcal/day, more than 70 food items left blank, or more than one food section left blank, other than dairy or meat sections), leaving a total of 333 women for the reproducibility analysis.

Maternal reports of NHSII adolescent diet were obtained from participants in the Nurses' Mothers Cohort Study. This study was begun in 2001 to investigate the effects of perinatal and early life exposure on adult disease and includes 35,830 mothers of NHSII participants. To select participants for the comparison of recalled high school diet from the NHSII women and their mothers, we randomly selected 400 NHSII participants who completed the initial HS-FFQ and whose mothers were respondents of the Nurses' Mothers Cohort Study. Those NHSII women who had cancer, heart disease, or asthma were excluded. We also excluded participants who were selected for the reproducibility substudy in order to reduce repondent burden. In addition, to obtain the best possible independent comparison of the HS-FFQ, only mothers who were early respondents to the Nurses' Mothers Cohort Study and who said they completed that questionnaire without the help of their daughters were included.

Among the 400 selected NHSII participants, 358 gave permission and provided current address information to contact their mother (90 percent). These mothers were then sent a HS-FFQ with instructions not to discuss their responses with their daughters before returning it. Of the 358 contactable mothers, 302 mothers completed the questionnaire (84 percent). Six mothers were not included in the analysis based on the established dietary exclusion criteria (described above). Another 24 mothers were excluded because they skipped two or more consecutive questionnaire pages. Thus, a total of 272 mothers were analyzed.

This study was approved by the Partners Institutional Review Board (IRB) at Brigham and Women's Hospital.

High School Food Frequency Questionnaire (HS-FFQ)

The HS-FFQ is a 124-item, self-administered food frequency questionnaire (available online at www.nurseshealthstudy.org). Questions included were how often, on average, NHSII participants consumed a specified food, beverage, or vitamin (described here on after, as "foods") when they were between the ages of 13 and 18, approximately high school age. This FFQ was modelled on other validated questionnaires conducted in the Nurses Health Study (NHS) and NHSII cohorts (11, 13, 14). Foods included were those commonly consumed by American adults during the years when participants were in high school (1960 to 1982), as assessed by earlier investigations (14). Foods of interest to cancer research such as major contributors of fat, fiber, and antioxident vitamins were included. We took secular changes in food formulation into account by using a NHSII participant's year of birth to assign different nutrient profiles for specific foods. Serving sizes were listed as natural units whenever possible (e.g. one apple, one glass of milk, and one slice of bread, etc.) and were otherwise based on the most common portion size reported by the United States Department of Agriculture's (USDA) National Food Consumption Survey 1977/1978 (NFCS) (15). The response choices for food items consisted of nine possible frequencies, ranging from almost never to six or more times per day. Questions about multi-vitamin and vitamin C supplement use had five possible response choices, ranging from a frequency of zero to 10 or more per week.

The nutrient intakes for each individual were calculated by multiplying the nutrient content of each food and supplement by the frequency of consumption relative to once per day, then summing the contribution from all foods and supplements (here, we use the term "nutrients" for convenience, recognizing that constituents like caffeine are not nutritive components). The

database for the nutrient analysis was constructed primarily from information provided by the U.S. Department of Agriculture Handbook and Bulletin for Foods consumed during the time period when NHSII participants were in high school (16-18).

Analysis

Nutrients were adjusted for energy intake using the residual method described by Willett and Stampfer, to account for variation in nutrient intakes due to total energy intake (19). Means and standard deviations were calculated to describe the intake and between-person variation of nutrient and food intakes. Nutrients were transformed by natural log to improve their normality for the correlation analyses (11).

To examine reproducibility, we calculated intraclass correlations for nutrients and Spearman rank correlations for foods from the two HS-FFQ's completed by the NHSII women. In addition, we evaluated the potential for confounding of reported high school diet by current diet by calculating the Pearson correlations between NHSII participants' nutrient intakes in the first HS-FFQ and their current nutrient intake in 1995 (the last adult diet measure prior to the 1998 HS-FFQ).

We also assessed the influence of misreporting of dietary intake on the reproducibility correlations. To identify under-reporting, we used the Goldberg cut-off for the ratio of energy intake to basal metabolic rate or physical activity level (PAL) (20, 21). The calculation of this cut-off has been reviewed by Black (20). We used a physical activity level (PAL) of 1.73 based on doubly-labelled water energy expenditure data for adolescent girls and values cited by Black to calculate the lower confidence limit (cut-off) of this PAL value (20). To further assess misreporting, we used the sex- and age-specific equations developed by the World Health

Organization (WHO) to calculate the ratio of reported intake to the predicted energy expenditure for NHSII participants when they were adolescents (22). To do this, the basal metabolic rate (BMR) for each participant was calculated based on her self-reported weight at age 18. This value was then multiplied by a physical activity level (PAL) of 1.5, based on data from the WHO assuming 2.5 hours of daily moderate physical activity (22). We next calculated the ratio of reported energy intake (using reported calories from the first administration of the HS-FFQ) to this predicted energy expenditure for each individual. Using these ratios, we classified women as "under-reporters" (ratio values in the lowest 20 percent in the distribution),"high-reporters" (ratio values in the top 20 percent in the distribution), and the remaining women as "acceptable reporters" for total energy intake and compared the reproducibility correlations between these three groups. Since physical activity level was the same for all participants, the percent cut-points for this second method depended on the ratio value of energy intake to basal metabolic ratio.

To evaluate the comparability of adolescent diet reported by NHSII participants and their mothers (maternal comparison), we calculated Pearson correlations for nutrients and Spearman rank correlations for foods. We also used Pearson correlations to assess associations between NHSII participants' current diets and their mothers' recall of their adolescent diet.

RESULTS

Reproducibility

The mean age of the NHSII participants at the first HS-FFQ administration was 43.8 years (range 33.6-53.3), thus, diet recall exceeded an average of 25 years in the past. The mean age of the subsample at the second HS-FFQ, approximately four years later, was 48.9 years (range 38.9-56.4). The women in both the first and second HS-FFQ administrations were similar across several demographic variables (table 1) and also similar to the entire NHSII cohort, from which they were originally sampled.

The nutrient correlations between the first and second NHSII participant recalls were moderate to good, with an average correlation of 0.65 and a range of 0.50 to 0.77 (table 2). Highly reproducible nutrients were total vitamin C ($r=0.77$), total vitamin B_2,($r=0.76$), and caffeine. ($r=0.74$). Nutrients measured with the least precision were alcohol ($r=0.50$) and vitamin B_{12}, both total ($r=0.51$) and without supplements ($r=0.52$).

The correlations between nutrients calculated from the 1995 current diet and from the first recall of high school diet were low with an average correlation of 0.20 and a range of -0.11 to 0.43 (table 2). Moreover, the correlations remained low using current diet as reported in 1999, one year after the first high school recall was administered (mean $r=0.20$ and range 0.01-0.44).

In our analysis of misreporting, we found no appreciable under-reporting on either the group or individual level using the Goldberg cutoff. Our calculated lower limit (the Goldberg cut-off for under-reporting) for the ratio of reported energy intake to predicted BMR was 1.70 for the overall group. Our study's group mean of 1.9 was higher than this cut-off, suggesting that the reported energy intakes of NHSII participants were reasonable in relation to under-reporting. On the individual level, our calculated lower limit ratio value was 1.26 and only 9.0 percent of

NHSII participants were below this lower limit. After excluding this 9.0 percent, our findings did not change appreciably (r=0.64) for nutrients. Using another method based on WHO cited values, the average nutrient correlations were similar for "under-reporters", r= 0.63 (20 percent prevalence); for "high-reporters", r= 0.66 for " (20 percent prevalence); and for "acceptable reporters", r=0.64 (60 percent prevalence).

To examine reproducibility further, we jointly classified nutrient intakes from the two administrations of the HS-FFQ into quintiles and calculated the percent of responses plus or minus one quintile. Eighty percent of the nutrient values from the second administration of the HS-FFQ were within one quintile of values from the first administration.

The correlations of foods were slightly lower than those for nutrients with an average of 0.60 and a range of 0.37 to 0.77. Highly reproducible foods were ice tea (r=0.77), diet soda with caffeine (r=0.76) and milk (r=0.76). Foods with the lowest reproducibility were diet soda without caffeine (r=0.37), onion eaten as a vegetable (r=0.42) and raw spinach (r=0.42) Individual correlations for all foods are available online at www.nurseshealthstudy.org. When grouped into food categories, the mean correlations between the first and second administration were good: dairy (r= 0.64), (non-dairy) beverages (r= 0.70), main dishes (r= 0.57), bread/cereals/grains (r=0.48), fruit (r= 0.67), and vegetables (r=0.64). Red meat, within main dishes, had a mean correlation of 0.52.

Comparison with Maternal Reports

The mean age of the mothers who responded was 73 years (range 58-89 years). The NHSII participants represented by the mothers were similar across several demographic variables to the 45,947 respondents of the first high school diet recall (table 1) and also similar to the entire NHSII cohort.

The nutrient correlations between the NHSII participants' and mothers' recalls were moderate with a mean of 0.40 and range of 0.13 to 0.59 (table 3). Nutrients with the highest correlations were animal fat and vegetable fat, both with a correlation of 0.51. Those with the lowest correlations were total calories (r=0.13), retinol (r=0.30) and monunsaturated fat (r=0.30). NHSII participants' current nutrient intakes, as assessed in 1995, were only weakly correlated with mothers' recall of their high school diet (mean nutrient correlation, r= 0.13).

Overall, the correlations for foods comparing mothers' reports with their daughters' reports were lower than for nutrients with a mean r=0.30 and a range of r=0.10 to 0.61 for foods. The foods with the highest correlations were ice tea (r=0.61) and orange juice (r=0.52). Those with the lowest correlations were brownies (r=0.10) and soda without caffeine (r=0.10). Individual correlations for all foods are available online at www.nurseshealthstudy.org.

DISCUSSION

In this study, we evaluated the reproducibility of a food frequency questionnaire (HS-FFQ) asking adult participants, at an interval of four years, about their high school diet consumed 15 to 35 years in the past. We also compared participants' recalls with high school diet information provided by their mothers. The mothers' reports were intended as independent estimates of their daughters' high school diets and thus a measure, though not ideal, of validity.

Reproducibility

Our results indicate moderate to good reproducibility for foods and nutrients and appeared consistent with the handful of studies to date that have examined remotely recalled adolescent diet. Previously, we examined the reproducibility of a shorter 24-item adolescent diet questionnaire administered two years apart to participants in the Nurses' Health Study (NHS), a cohort that is similar to but older than the women in NHSII (12, 13). We reported an average correlation of 0.57 for 24 foods (range of 0.38 for beef to 0.73 for orange juice) and 0.48 for nutrients (range of 0.34 for vitamin E to 0.68 for cholesterol). Wolk et al examined the short-term reliability (9-12 months) of adolescent diet recalled over 20 years later by healthy control subjects in a Swedish case-control study and reported a correlation of 0.46 for both foods and nutrients for a 45-item food frequency questionnaire (23).

The influence of current diet is an important possible source of bias for the assessment of remote diet. For instance, our reproducibility results could potentially be overestimated if NHSII participants simply reported their current diet at both administrations of the questionnaire. However, the low correlations between current and recalled diet (r=0.20, for nutrients) suggest our reproducibility results are not substantially inflated by current adult diet. The timing of

assessment of current diet, whether before or after the administration of the HS-FFQ, also did not influence the results.

Other published reports have reported a larger correlation between current diet and remotely recalled diet (24-27). For instance, Bakkum et al reported a 0.72 food correlation for men and 0.64 correlation for elderly men and women (25). Wu et al reported a food correlation of 0.54 for men and 0.56 for women (24). One explanation for this difference is that in some studies, participants' current diets were assessed at the same time as their recalled diets, which could have influenced recall and artificially inflated their results due to correlated error (24, 25, 27). Alternatively, these reports may truly reflect greater stability of adult diet over time.

Our low correlations between current and recalled diet together with the stronger correlations between two recalls of high school diet, suggest that participants may have eaten differently during high school (13). For instance, the greatest decrease in nutrients was for fats, with a 60 percent decline for total saturated fat intake, which is consistent with national trends. Reported calories from total fat also decreased from 40 percent to 29 percent and calories from carbohydrates and protein increased. Because of presumed diet stability, some have suggested the use of current diet as a surrogate measure of past diet (7, 27). However, our results imply that the best measure of past adolescent diet (in the absence of original data) is recalled, not current diet, a conclusion consistent with other, previous investigations (8, 13, 28).

Dietary data may be prone to systematic underreporting of food and nutrient intake and to a lesser extent, systematic over-reporting (20, 29). We did not find evidence for under-reporting using the Goldberg cut-off for the ratio of energy intake to basal metabolic rate. Further, our analysis did not indicate appreciable differences in the correlations for subjects classified as "under", "high", and "acceptable" reporters using 20 percent cut-offs for energy intake.

Correlated error is likely present between the two NHSII HS-FFQ reports, which will tend to overestimate the reproducibility correlations. This underlies the importance of having an independent estimate of intake, which was the intention of comparing the mothers' reports with their daughters' reports in this study.

Maternal Comparison

The correlations for the maternal comparison were modest for foods and moderate for nutrients. Other studies reported similar or weaker results. Wolk et al examined adolescent diet recalled by study participants with the adolescent diet remotely recalled by their adult siblings as a proxy external comparison (23). The average correlation was 0.30 for foods and nutrients. Several studies have examined the validity of distant diet (> 10 years), comparing diet that was recalled with diet recorded at the time of interest (often called original diet) and have been reviewed elsewhere (10, 13). Dwyer et al examined the validity of adolescent diet by using diet histories conducted during childhood and found a low median nutrient correlation of 0.12 for recalled foods eaten at age 18 (30). This low correlation could be due to the rather crude original assessment of diet. Other studies addressing the validity of diet during adulthood (recalled 11 to 24 years in the past), have reported average correlations that were moderate for food intakes (range of average correlations, 0.29-0.40) and higher for nutrient intakes (range of average correlations, 0.23 to 0.59) (24-27, 31, 32). Though we do not have original diet, our correlations appear consistent with these reports.

Correlated error between NHSII reports and mothers' reports could lead to overestimation of validity if, for example, the mothers discussed their responses with their daughters before returning the questionnaire. We took precautions to minimize this possibility (as detailed in the

Methods section). Although we cannot completely exclude this bias, we believe it is unlikely that a large portion of mothers ignored our instructions and discussed their responses with their daughters. Also the daughters completed the questionnaires over four years earlier and it is unlikely that they remembered specific responses.

An important limitation of this study is that we did not have actual diet information from participants when they were in high school. The mothers' reports provided some measure of validity, though not a perfect one (33). The fact that mothers may not have been aware of all their nurse-daughters' food habits outside the home will result in error in reporting. For instance, the mothers tended to under-report caffeine and fat more than fruit and vegetable-related nutrients compared to the NHSII participants' reports, which supports the idea that they did not know all that their daughters were eating. In addition, mothers' fading memories may have also contributed to error in reporting of diet, which would attenuate correlations. In making this comparison between mothers' and daughters' reports, we recognize that there are virtually no true measures of absolute intake for adolescent diet eaten decades in the past, only imperfect standards. This underscores the methodological challenges of evaluating retrospective recall of diet in the distant past. In the absence of actual diet information from the NHSII participants, a more rigorous validation study would be desirable - for example, by administering the same questionnaire to a group of participants for whom diet was recorded when they were in high school.

Lastly, the NHSII participants represented in the reproducibility and maternal comparison components of this study consisted largely of Caucasian women and are not necessarily generalizable to men or other women with different ethnic backgrounds, age, or education.

However, our study subsample was representative of the full NHSII cohort with respect to age, BMI, smoking status, and reproductive variables.

This study also has several strengths over other investigations in this area. First, it is one of the few that has examined diet during high school. Adolescence may be a particularly important time for the study of chronic diseases, and remains a relatively unexplored area of investigation. The period of time between repeated questionnaire administrations was long enough (four years) so that it is unlikely that participants would have remembered their initial responses and have been influenced by them in the second administration. The potential of recall bias in estimating food and nutrient intakes underlies the importance of prospective studies such as this present study, in which data is collected before disease occurs. Lastly, as an implication of our results, the low correlations between recalled high school diet and current diet suggest that our information on high school diet is almost independent of data on adult diet, and thus, the high school dietary information from it has the potential to add new insights on disease etiology. While further studies are warranted, our findings suggest that this food frequency questionnaire completed during adulthood, provides a reasonable record of diet during adolescence for use in assessing associations with adult disease.

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TABLE 1. Characteristics of all Nurses' Health Study II (NHSII) participants who responded to the High School Food Frequency Questionnaire (HS-FFQ) compared to those selected for the reproducibility and maternal comparison studies

	All HS-FFQ Respondents	Reproducibility Substudy	Maternal Comparison Substudy
	(n=45,947)	(n=333)	(n=272)
Mean age (yrs) *	44	49	47
Mean BMI (kg/m^2) at age 18, at baseline †	21	21	21
Mean BMI (kg/m^2) ‡	26	26	25
Mean age at first birth (yrs) ‡	26	26	27
Premenopausal (%) ‡	84	84	92
Nulliparous (%) ‡	7	9	9
Currently smoke (%) ‡	9	6	7

* Reported value in 1998 for all respondents and for participants in maternal comparison substudy and value reported in 2002 for participants in reproducibility substudy

† Value as reported in 1989

‡ Value as reported in 1997

TABLE 2. Nutrient correlations between two recalls of high school diet (using the HS-FFQ) and between recalled high school diet and current diet, Nurses' Health Study II (reproducibility substudy)

Nutrient *	1st HS-FFQ (1998) Mean (n=333)	2nd HS-FFQ (2002) Mean (n=333)	Current Adult Diet (1995) Mean (n=308) †	Intraclass Correlation between 1st and 2nd HS-FFQ's ‡	Pearson Correlation between 1st HS-FFQ and 1995 Current Diet ‡
Total calories (kcal)	2766	2669	1752	0.69	0.43
Total fat (g)	124	123	57	0.62	0.20
Animal fat (g)	79	79	33	0.66	0.21
Vegetable fat (g)	44.8	45	24	0.64	0.16
Total saturated fat (g)	49	49	20	0.66	0.24
Total monounsaturated fat (g)	44	44	22	0.60	0.23
Total polyunsaturated fat (g)	20	20	10	0.58	0. 07
Total trans fat (g)	7	7	3	0.62	0.19
Cholesterol (mg)	439	434	225	0.59	0.18
Protein (g)	106	106	86	0.57	0.23
Carbohydrates (g)	312	313	240	0.58	0.19
Glycemic index, bread	78	78	77	0.60	0.29
Glycemic load, bread	245	245	183	0.58	0.24
Total fructose (g)	70	70	43	0.65	0.17
Dietary fiber (g)	21	21	20	0.67	0.38
Vitamin A (μg, RE) §	1860	1865	2159	0.71	0.29
w/o supplements (μg)	1679	1718	1515	0.66	0.32
Retinol (μg)	929	880	1033	0.63	0.16
w/o supplements (μg)	746	733	518	0.52	0.06
Beta carotene (μg)	3810	3969	5293	0.72	0.32
Vitamin E (mg): total	13	13	47	0.62	-0.11
w/out supplements	13	13	8	0.61	0.14
Vitamin C (mg): total	164	164	326	0.77	0.28
w/o supplements	143	145	142	0.72	0.43
Riboflavin, B_2 (mg)	2	2	4	0.76	0.17
w/o supplements (mg)	2	2	2	0.72	0.18
Pyridoxine, B_6 (mg)	2	2	10	0.73	0.07
w/o supplements (mg)	2	2	2	0.64	0.25
Vitamin B_{12} (μg)	9	8	10	0.52	0.08
w/o supplements (μg)	8	8	6	0.51	0.15
Vitamin D (μg)	9	9	10	0.71	0.16
w/o supplements (μg)	8	8	6	0.68	0.22
Total folate (μg)	327	328	485	0.72	0.20
w/o supplements (μg)	317	321	321	0.67	0.33
Calcium (mg)	1081	1101	1036	0.73	0.13
Iron (mg)	14	14	25	0.61	-0.02
Caffeine (mg)	91	82	210	0.74	0.22
Alcohol (g)	0.2	0.3	3	0.50	0.14
			Average	**0.65**	**0.20**

* All nutrients are energy-adjusted an nutrients for the correlations are also log-transformed

† Only 308 women who had responded to the 1995 NHSII (current) adult diet questionnaire had also completed the 1998 HS-FFQ

‡ All correlations larger than 0.11 are significant at the 0.05 level. Also, all p-values are two-sided

§ RE, Retinol Equivalents

TABLE 3. Nutrient correlations of high school diet reported by adult women and their mothers, Nurse' Health Study II (maternal comparison substudy)

Nutrient *	1st HS-FFQ Mean (n=272)	Mothers' HS-FFQ Mean (n=272)	Pearson correlation between 1st HS-FFQ versus Mothers' HS-FFQ †
Total calories (kcal)	2807	2289	0.13
Total fat (g)	124	99	0.32
Animal fat (g)	77	61	0.51
Vegetable fat (g)	47	37	0.51
Total saturated fat (g)	48	39	0.47
Total monounsaturated fat (g)	44	35	0.30
Total polyunsaturated fat (g)	21	16	0.35
Total trans fat (g)	7	6	0.45
Cholesterol (mg)	426	348	0.34
Protein (g)	107	84	0.42
Carbohydrates (g)	312	253	0.33
Glycemic index, bread	78	77	0.43
Glycemic load, bread	245	196	0.38
Total fructose (g)	70	58	0.31
Dietary fiber (g)	20	17	0.35
Vitamin A (μg, RE) ‡	1801	1710	0.42
w/o supplements (μg)	1644	1426	0.42
Retinol (μg)	846	879	0.30
w/o supplements (μg)	688	595	0.32
Beta carotene (μg)	3833	3307	0.33
Vitamin E (mg)	13	10	0.38
w/o supplements (mg)	13	10	0.36
Vitamin C (mg)	160	153	0.43
w/o supplements (mg)	137	125	0.39
Riboflavin, B_2 (mg)	2	2	0.42
w/o supplements (mg)	2	2	0.59
Pyridoxine, B_6 (mg)	2	2	0.41
w/o supplements (mg)	2	2	0.43
Vitamin B_{12} (μg)	8	7	0.43
w/o supplements (μg)	8	7	0.42
Vitamin D (μg)	9	9	0.48
w/o supplements (μg)	8	7	0.46
Total folate (μg)	322	276	0.47
w/o supplements (μg)	315	264	0.49
Calcium (mg)	1103	893	0.47
Iron (mg)	15	11	0.47
Caffeine (mg)	83	51	0.47
		Average	**0.40**

* All nutrients are energy-adjusted and nutrients for the correlations are also log-transformed
† All p-values for Pearson correlations are two-sided and are significant at the 0.05 level
‡ RE, Retinol Equivalents

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